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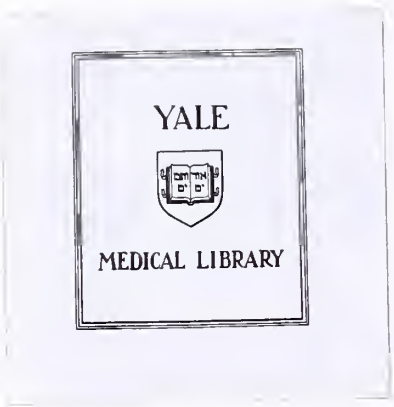
THE MANAGEMENT OF CYSTINURIA

by

EDWARD CHARLES HALPERIN

1979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THE MANAGEMENT OF CYSTINURIA

by

Edward Charles Halperin

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirement for the degree of Doctor of Medicine

1979

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This thesis is dedicated to Barry Adler (1952 - 1975). He was a gentle scholar and my faithful friend.

Acknowledgments

The idea for this thesis was originally generated in a discussion with Dr. Leon E. Rosenberg. Dr. Rosenberg has continued, throughout this work, to be a source of instruction and support. Dr. Samuel O. Thier has given direction and guidance. The role models both these gentlemen have provided far exceed the conventional limits of "thesis advisors".

I have benefited from the criticisms, insights, and assistance of Drs. A.R. Feinstein and E. Prien, Jr.. The staff of the medical records room of Yale-New Haven Hospital was consistently courteous and efficient in providing me with the raw material for my research.

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ECH

Bethesda, Maryland
20 January 1979

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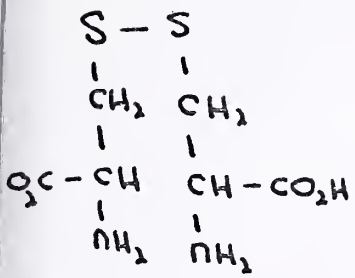
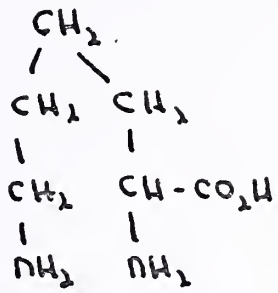
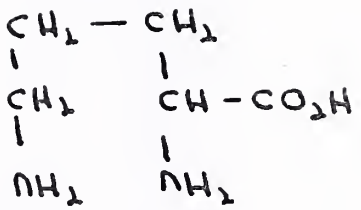
Pertinent Chemical Structures



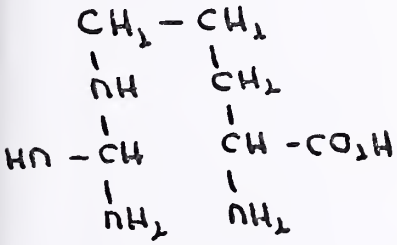
cystine



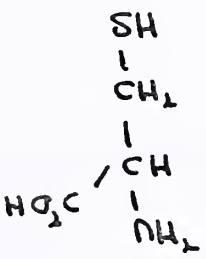
lysine



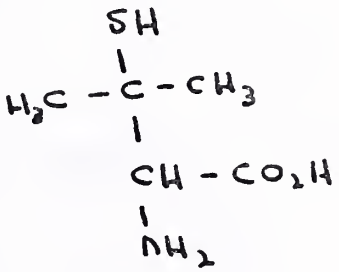
ornithine



arginine



cysteine



penicillamine

I. CYSTINURIA: AN OVERVIEW

A. Introduction

Cystinuria is an autosomal recessive inherited disorder of cystine and dibasic amino acid transport. The transport defect affects the epithelial cells of the renal tubules and the gastrointestinal tract. Because of the renal defect, the amino acids cystine, lysine, arginine, and ornithine are excreted in great excess in the urine. Excessive urinary quantities of cystine, the least soluble of naturally occuring amino acids, predisposes to the formation of renal, ureteral, and bladder calculi. The major causes of morbidity and mortality in this disorder are the sequelae of this stone formation: renal and ureteral colic, urinary tract infection, and compromise of renal function. The defect of gastrointestinal tract epithelium is expressed by elevated stool levels of dibasic amino acids and their breakdown products.

B. Historical Landmarks in the Study of Cystinuria

1. Renal Defect

William Hyde Wollaston, MD, Secretary to the Royal Society of London, came before that body in July of 1810 to announce a new discovery. Wollaston wished "to make known the existence, and to describe the leading properties of a new species of urinary calculus for the human bladder." The English physician had obtained two specimens of the new material. The first was from the bladder of a five

year old boy - the brother of a colleague. The second specimen had been located in the collection of Guy's Hospital - having been extracted from a thirty-six year old man named William Small.

Wollaston carefully described the appearance of these stones. He found them to be soluble in either strong acid or alkali. The physician concluded that the material was

> an oxide; and since both the calculi that have been observed have been taken from the bladder, it may be convenient to give it the name of cystic oxide, which will serve to distinguish it from other calculi; and as this is unlike any other term at present employed in chemistry, it is to be hoped that it will not be thought to require any alteration.[110]

Contrary to Wollaston's wish, the term "cystic oxide" did require alteration - for the compound was not an oxide. The name which came to be universally adopted was suggested by Berzelius:[41] cystine. Unfortunately, by adopting the Greek root for bladder (kystis), Berzelius perpetuated an error of physiology. Cystine is excreted by the kidneys and does not have its origin in the bladder.

In 1824 Stromeyer's discovery of cystine crystalluria was published.[75] When, over sixty years later, Von Udranszky and Bauman found cadaverin and putrescine in the excretea of a cystinuric, they suggested that the defect in cystinuria involved more than that of a single amino acid.[86] Garrod remarked, in his 1908 Croonian lectures, that the presence of cadaverin and putrescine in the urine suggested excessive excretion of lysine and arginine.[41] This "diaminuria", he said,

"might be an outcome of the same error of metabolism as cystinuria...." Using microbiologic assays, Yeh and his associates demonstrated marked increases in urinary excretion of cystine, lysine, and arginine by an eight year old patient.[111] Stein later used chromatographic techniques to confirm Yeh's findings and added ornithine to the list of amino acids excreted in excess by cystinurics.[101]

In their classic 1951 paper, Dent and Rose synthesized the preceeding findings by pointing out that cystine, arginine, lysine, and ornithine each had two amino (or guanidine) groups separated by four to six carbon, or sulfur atoms.[24] Normally, these amino acids are filtered and then reabsorbed in the tubule. They suggested that

> as a result of an inherited defect of the renal tubules, he (the cystinuric) is only able to reabsorb from the glomerular ultrafiltrate about one-half of the cystine present, and a small but unknown proportion of the lysine and arginine. These substances are therefore concentrated in the urine to a degree which may reach twentyfold of normal...The cystine is very insoluble, and the urine passed is therefore supersaturated when excreted, and tends on standing to deposit the characteristic crystals, especially when the urine is acid and the cystine is therefore near its isoelectric point.[24]

Dent and Rose's hypothesis had implications beyond its correct explanation of the aminoaciduria in cystinuria. The hypothesis suggested that renal tubular absorption was accomplished by specific mechanisms directed by the genome. The idea suggested an entire class of inborn metabolic diseases: the "inborn errors of transport."

2. Intestinal Defect

Von Udranszky and Bauman in 1889 observed that the diamines, cadaverine and putrescine, decarboxylation products of lysine and arginine, were present in large amounts in the feces of a cystinuria patient.[86] Garrod mentioned this observation in his Croonian lectures to support his concept of biochemical heterogeneity in cystinuria.[41] Over fifty years later, Milne performed experiments which demonstrated an intestinal absorption defect for the dibasic amino acids in patients with cystinuria.[72] Asatoor reported additional experimental evidence in support of an intestinal transport lesion.[7] Thier, et al have confirmed this work by in vitro studies of intestinal transport using jejunal biopsies.[104,106]

3. Genetics

Marcet noted the familial occurrence of cystinuria eight years after Wollaston's original report.[96] Later in the nineteenth century, the chronicity of cystinuria was suggested in a case reported by Sir Henry Thompson. Thompson described, in 1870, an 81 year old man for whom a cystine calculus was crushed. The patient had passed a stone of a similar chemical nature thirty-nine years previously.[41]

Garrod appreciated the familial and chronic nature of the disease and discussed cystinuria among the inborn errors of metabolism.[41] In 1953, Harris and co-workers analysed patients' pedigrees, using quantitative urine amino acid determinations, and concluded that cystinuria is inherited

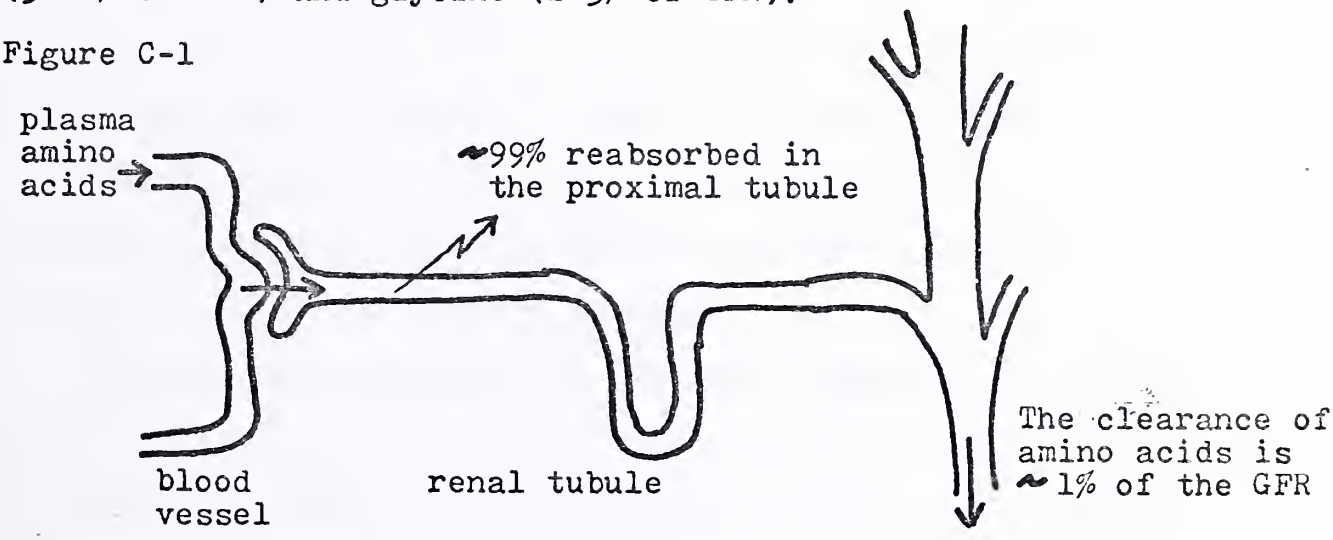
as an autosomal recessive disorder. The genetics of cystinuria, however, have proven to be more complicated than simple autosomal recessive inheritance. Rosenberg and his colleagues have used various laboratory and clinical measurements to indicate that cystinuria is at least three biochemically distinct inheritable diseases.[93]

C. Pathophysiology

1. Renal

Cusworth and Dent have demonstrated that normally more than 99% of filtered amino acids are reabsorbed by the renal tubule[21] (see Figure C-1). This reabsorption occurs, for the most part, in the proximal tubule. Amino acid clearances are, therefore, less than 1% of the glomerular filtration rate (GFR) with two exceptions in man: histidine (5-10% of GFR) and glycine (2-5% of GFR).[112]

Figure C-1


plasma amino acids
~99% reabsorbed in the proximal tubule
The clearance of amino acids is ~1% of the GFR
blood vessel
renal tubule

It is known from clinical work that there are a variety of aminoacidurias. Many of these disorders are caused by renal defects specific for several groups of amino acids. These findings have prompted the search for specific transport systems responsible for reabsorption of filtered amino acids.

It was postulated by Dent and Rose that arginine, cystine, lysine, and ornithine were reabsorbed by a common renal transport system.[24] Absence of this system in the

homozygote would account for phenotypic cystinuria. This hypothesis has been tested experimentally.

Rosenberg et al studied the transport of arginine, cystine, lysine, and ornithine in an experimental model of male Sprague-Dawley rat kidney cortex slices incubated in buffer.[84] Arginine, cystine, and lysine were concentrated in kidney slice cells against chemical concentration gradients during thirty minute incubation studies. Mutual competitive inhibition between arginine, lysine, and ornithine were demonstrated. Cystine, however, did not appear to share in this inhibition - although it was concentrated. These experiments suggested that while arginine, lysine, and ornithine shared a common transport mechanism, cystine uptake was by an independent mechanism.

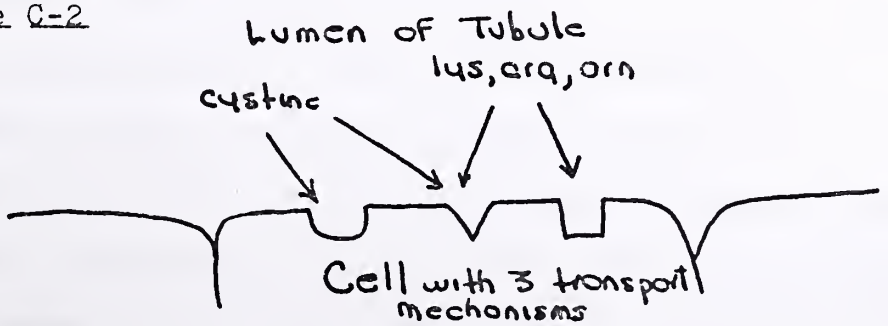
This work was pursued, by the same research group, with human renal tissue obtained by open biopsy at the time of abdominal surgery.[38] Kidney cortex slices were incubated in buffer. Radioactive amino acids were used to study transport. The kidney slices from cystinurics took-up arginine and lysine, after thirty minutes of incubation, to approximately half the concentration of controls. The uptake of cystine was, however, similar to that of controls.

Further support for the separate nature of renal transport processes for cystine and dibasic amino acids came from Crawhall's study on renal clearance of amino acids in nine cystinurics.[18] The ratio of cystine clearance

to GFR varied between one and two. In six out of nine patients, cystine clearance exceeded GFR. This suggested some efflux from the renal tubule cell into the lumen of the tubule. The clearances of the dibasic amino acids were found not to parallel the clearances of cystine. For example, the ratio of lysine clearance to GFR ranged from 0.44 to 0.78. The situation could be explained by separate carrier mechanisms.

In experiments with slices of human kidney cortex from two control subjects and two cystinurics, Rosenberg et al demonstrated two distinct transport systems for lysine.[82] These systems differed in affinity and capacity. A single transport system for cystine was demonstrated. We may synthesize the preceeding experimental and clinical findings by postulating that dibasic amino acid transport in the human kidney depends on more than a single mechanism. The model shown in Figure C-2 attempts to account for a system responsible for classical cystinuria as well as separable cystine and dibasic amino acid transport systems.

Figure C-2



Segal and Smith have provided additional evidence for distinct transport systems by observing that cystine uptake by newborn rat kidney cortex *in vitro* is impaired

and does not reach the normal adult level until fifteen days of age.[92] Lysine uptake by the cortex of the newborn, however, is comparable to that observed in adults. These developmental differences argue against the concept of only one common transport process for lysine and cystine. If only one process existed, it would be difficult to explain the developmental findings.

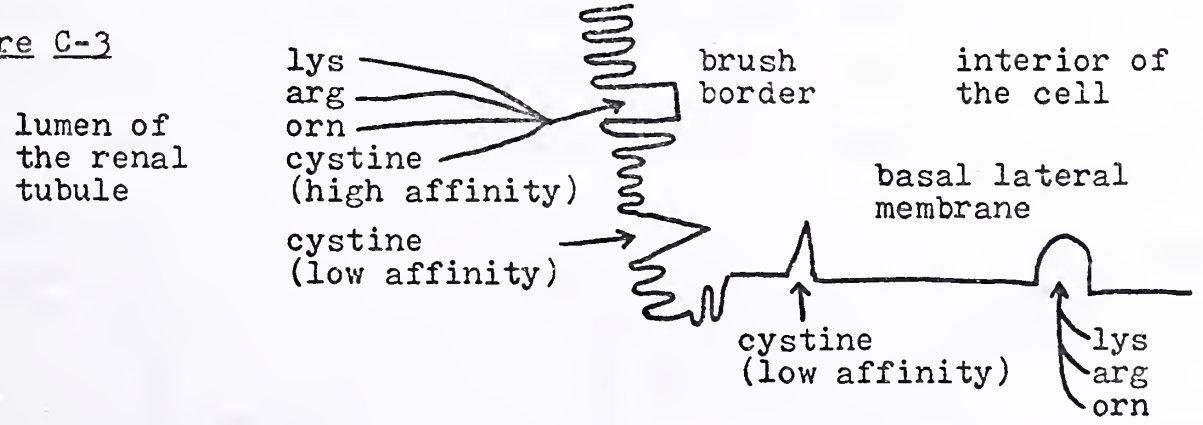
The above mentioned experimental evidence would suggest the theoretical possibility of clinical hyperdibasic-aminoaciduria without cystinuria as well as the converse. Whelan has reported the occurence of elevated excretion of arginine, lysine, and ornithine without cystinuria in thirteen of thirty-three kin in a French Canadian pedigree.[109] Oyonagi has reported two siblings with a similar biochemical picture.[76] The converse situation was reported by Brodehl: isolated hypercystinuria was observed in two siblings.[12]

The model offered in Figure C-2 remains controversial. Silbernagl and Deetjen have reported that in microperfusion experiments, the dibasic amino acids are able to inhibit cystine reabsorption.[96] This may be explained by at least one common luminal transport system. It may also, however, be explained by Greth's demonstration that cystine can enter the renal tubule cell via the basal lateral membrane in rats under conditions where luminal transport does not occur.[45] The transport phenomena observed in the rat kidney cortical slice experiments may have been largely by way of

the basal lateral membrane. We may, therefore, have learned very little about luminal brush border transport by cortical slice experiments.[88] Silbernagl's microperfusion study may be closer to the truth - at the brush border.

Segal has attempted to resolve this problem by studying the uptake of cystine at the membrane locus of transport.[91] He has used vesicles prepared from rat kidney brush borders. In 1977, Segal's group reported that cystine uptake appears to occur by two distinct transport systems. A high affinity system is inhibited by the dibasic amino acids. The low affinity system is unaffected by the dibasic amino acids. This low affinity system appears to correspond to that observed by studying amino acid transport with cortical slices. We may represent these results in Figure C-3.

Figure C-3



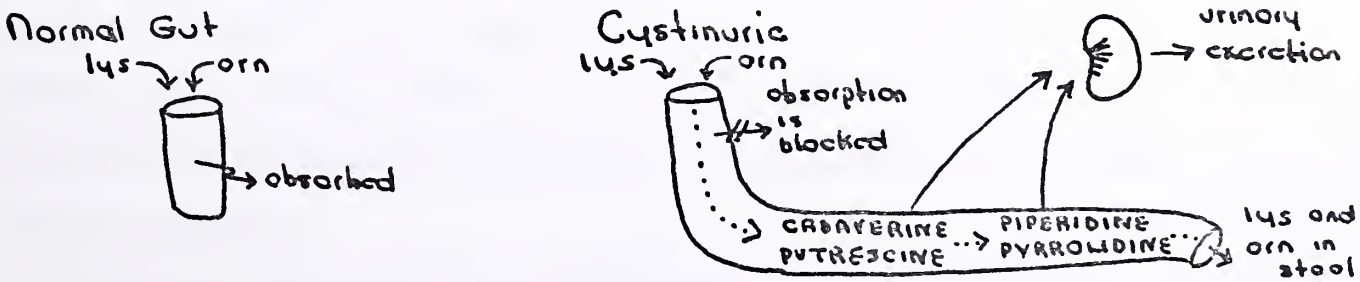
As the preceeding discussion indicates, the pathophysiology of cystinuria is not precisely defined. Additional areas of controversy include the explanation of cystine clearance exceeding GFR in dogs[11] and humans[18] (suggesting cystine secretion). The role of cysteine in the efflux mechanism of the renal tubule cells is not clearly defined. A cysteine leak into the lumen has been suggested.

2. Intestinal

Milne and co-workers studied the effects of oral doses of lysine and ornithine in homozygous cystinurics and in normal control subjects.[72] The amino acids were less completely absorbed by the cystinurics and a considerable fraction appeared in the feces. In contrast, in normal subjects absorption was usually complete.

Colonic bacteria converted unabsorbed lysine and ornithine to cadaverine and putrescine. These occasionally occured in sufficient concentration to be detectable in the urine of cystinurics. The greater fraction of the intestinally absorbed diamines are converted to piperidine and pyrrolidine. Output of these compounds in cystinuric patients, following lysine or ornithine ingestion, exceeded that of normals. Milne's experiments suggested an intestinal transport defect in cystinuria. (See Figure C-4)

Figure C-4



Asatoor, Lacey, London, and Milne soon extended their experiments to include arginine.[7] An intestinal absorption defect for arginine was demonstrated in cystinurics. After ingestion of arginine, the feces of cystinurics contain considerable amounts of the bacterial breakdown product citrulline. Some of this product appears in the urine.

The metabolite pyrrolidine is excreted in greater quantity by cystinurics than normals in the twenty-four hours following arginine ingestion.

Detailed investigations by Thier et al defined the nature of the intestinal defect.[104,105] Jejunal mucosa was obtained via Rubin tube from normal and cystinuric subjects. Intestinal mucosa from four normal volunteers concentrated lysine thirteen fold and cystine four and one-half fold. An initial group of cystinurics failed to concentrate either of these amino acids significantly. Furthermore, lysine accumulation was inhibited by arginine or cystine and cystine uptake was inhibited by lysine. Mucosa from a subpopulation of cystinurics did absorb cystine - a point which will be considered later. The transport mechanisms were found to be energy dependent.

The experimental evidence indicates an intestinal absorption defect in cystinuria. A single transport system appears responsible for absorption of cystine and the dibasic amino acids in the gut. Absence of this system explains the biochemical findings in the affected individual.

D. Clinical Aspects

Several individuals have attempted to estimate the incidence of cystinuria. Lewis[62] tested the urines of 10,000 college students with the nitroprusside reaction for cystine. He found that 1/600 students had a positive reaction. This estimate is almost certainly too high. The nitroprusside reaction is positive if urinary cystine is greater than 75mg/liter and, hence, cannot distinguish between homozygotes and many heterozygotes. In a 1968

review atricle, Crawhall calculates a homozygous cystinuria incidence rate of 1/20,000 based on the assumption that the commonly recessive form of cystinuria is about twice as frequent as the incompletely recessive form.[20] Crawhall's estimate is supported by the figures from the Massachusetts Metabolic Disorders Screening Program. This newborn screening program has a cystinuria incidence of 1/17,738 in a population of 141,903 infants studied.[47]

The first clinical expression of cystinuria usually occurs in the second or third decades of life.[86,106] The disease may, however, present in infancy or old age. The common presenting signs are those of urolithiasis: gross haematuria, abdominal or flank pain, and renal colic with or without stone passage.[68] Urinary tract infection may also occur. Obstructing stones can compromise renal function and lead to renal failure. Hypertension is associated with cystinuria in 10% of cases.[22] There are no physical stigmata.

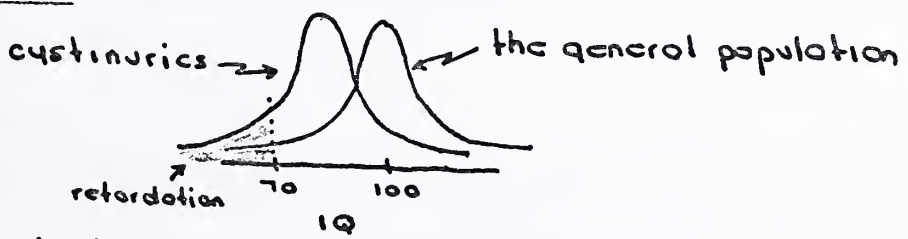
Cystinuria occurs equally in both sexes. Males have been reported to be more severely affected, perhaps due to the greater likelihood of urethral obstruction.[106] A recent Mayo Clinic study, however, found that parameters of morbidity and severity of cystinuria were not significantly different in men and women.[22]

Cystine stones constitute about 1% of all upper urinary tract stones.[68] The stones are radiopaque due to the density of the sulfur region.[93] About one-half of stones recovered from cystinurics are pure cystine.[10] Another 45% to 50% are cystine mixed with other compounds.[10]

One or two percent of recovered stones contain no cystine. Some physicians, however, believe the incidence of non-cystine stones in cystinuria is actually much higher than two percent.[78]

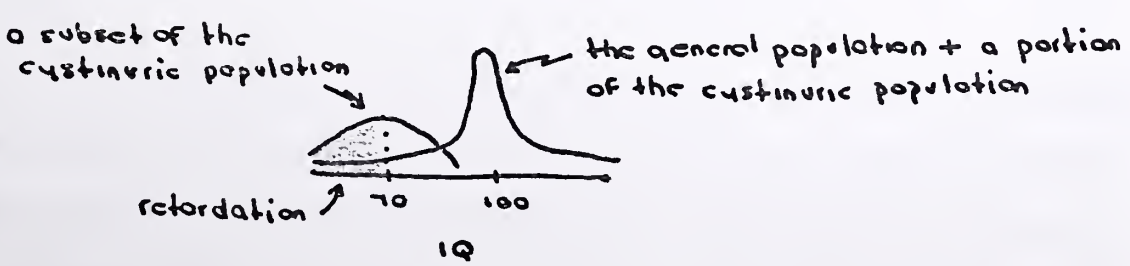
Cystinuria has been associated with several other condition. The disease may occur with hyperuricemia[71] and uric acid nephrolithiasis.[108] Cystinuria is significantly more frequent in a population of patients with mental illness or retardation than in the general population.[90] It has been postulated, without experimental confirmation, that the amino acid transport defect involves the brain. If cystinuria lowered the IQ of all cystinurics, we could explain the increase in mental retardation as a shift of the IQ distribution curve to the left. (see fig. D-1)

Figure D-1



Cystinuria is a heterogeneous disease and it may be that some genotypes are associated with abnormal IQ distribution while other genotypes do not affect IQ. (see fig. D-2)

Figure D-2



Since cystinurics do not differ significantly in their

intelligence from their normal siblings or intelligence test norms, the situation suggested by figure D-2 is more likely.[43]

One might postulate that impaired absorption and retention of essential amino acids could lead to deficiencies in the cystinuric individual's growth and development. Studies looking at the effect of cystinuria on final height are not in agreement. Andrews noted, in 1952, that in his "experience cystinurics are, in general, persons of somewhat less than average stature" and that they "have always been of somewhat slight build."[4] In 1963, Colliss et al studies a population of cystinurics and found their mean height to be 2.5cm less than that of normal subjects.[16] A Mayo Clinic study found no significant difference between the mean height of cystinuric patients and that of normals.[22]

E. Diagnosis

Any patient with urolithiasis who has passed renal stones in childhood, who has many recurrences, or who has a family history of renal stones deserves a work-up for cystinuria. The relatives of a diagnosed cystinuric should be screened in order to identify new and unsuspected cases.

The suspicion of cystinuria may be confirmed by a simple and inexpensive microscopic examination of urinary sediment. The presence of typical, hexagonal "benzene-ring" crystals is diagnostic. The crystals may be difficult to identify in

dilute or alkaline urine. If glacial acetic acid is used to lower urine pH to about 4 and the refrigerated urine allowed to stand overnight, crystals may be found in the centrifuged sediment.[26]

A simple screening test for cystinuria is the cyanide-nitroprusside test. Five ml of urine is alkalinized with 5 drops of NH_4OH. Two ml of 5% NaCN is added and the solution allowed to stand for ten minutes. If, on addition of drops of 5% Na Nitroprusside a stable purple-red color appears the test is read as positive.[28] The color should be compared to a sample of normal urine to which cystine has been added.[106] A positive test may also be seen in acetonuria, homocystinuria, and a new metabolic disorder characterized by the excretion of cystine-β-mercaptolactate mixed disulfide.[86]

Diagnostic confirmation depends on the demonstration of the characteristic pattern of amino acids in the patient's urine. Paper chromatography or electrophoresis is used to identify cystine, lysine, arginine, and ornithine in excess quantities. Column chromatography is used if quantitative amino acid determination is desired. Homozygotes usually excrete in excess of 400mg of cystine per day.

On roentgenologic examination, cystine stones are smooth. They are often multiple and may coalesce to form staghorn masses. The stones may decrease in size or disappear if effective therapy is instituted.

When stones are available for examination, the diagnosis should not be missed. Cystine stones are

honey yellow to yellow-white in color and may have a pearly luster. They consist of porous aggregates of crystals.[77]

F. Genetics

Harris and his colleagues have made a major contribution to our understanding of the genetic of cystinuria.[49-51] These workers, estimating cystine polarographically and dibasic amino acids by microbiologic assays, found two types of families of cystinuric individuals. In one group of families the parents and children of the cystinuric patient excreted normal amounts of amino acids. This type of inheritance was called "recessive cystinuria." In the other group of families, parents and children of patients were frequently found who had moderately increased cystine and lysine excretion with arginine and ornithine excretion being normal or slightly raised. This situation was called "incompletely recessive cystinuria." (see fig. F-1)

Figure F-1

The Harris Model

recessive incompletely recessive

- normal amino acid excretion
- cystinuria
- increased cys, increased lys

The suggestion of genetic heterogeneity in cystinuria was supported by Thier, et al in their investigation of amino acid transport by jejunal mucosa *in vitro*.[104-105] Ten of

twelve stone forming cystinurics had absent uptake of cystine, lysine, and arginine by jejunal mucosa. Two patients with typical cystinuria had normal intestinal transport of cystine with reduced transport of arginine and lysine. The findings were not associated with differences in urinary amino acid excretion by homozygotes.

Three genetically distinct types of cystinuria were defined by Rosenberg and co-workers.[83] They utilized *in vitro* transport studies with gut mucosa, oral loading studies with cystine, and patterns of urinary excretion of cystine and dibasic amino acids in heterozygotes to indicate three biochemically distinct diseases (named types I, II, and III). Homozygotes of all types excrete excessive urinary cystine and dibasic amino acids. The distinctions are found in gut transport and heterozygote expression. Type I, corresponding to Harris' "recessive" type, lacks active transport in the gut for disbasic amino acids. Heterozygotes excrete normal amounts of the four amino acids in the urine. Type II has impaired intestinal transport of lysine but cystine transport is present. Heterozygous type II's excrete definitely increased amounts of the four amino acids. Homozygous type III individuals have active intestinal transport of cystine, lysine, and arginine. These individuals can, therefore, absorb an oral load. Urinary excretion of the four amino acids is only moderately increased in heterozygotes for type III. Harris' "incompletely recessive"

cystinuria includes types II and III.

While the preceeding data suggests at least three mutations resulting in phenotypic cystinuria, it does not determine if the observed heterogeneity is due to allelic or nonallelic mutations. Marin's group from Toronto[69], Rosenberg in New Haven[80], and Hershka in Israel[115] have described several fascinating families which shed light on this question. Marin's family CyI (Figure F-2) presented with a phenotypic cystinuric female II-1. Her brother, II-4, and father, I-1, were heterozygotes type II. The proband's mother, I-2, and sisters, II-2 and II-3, had normal twenty-four hour urinary amino acid excretions. Proband II-1 had urinary amino acid excretions in amounts midway between type II heterozygotes and homozygous abnormals. Her intestinal handling of amino acids was between that of a +/II heterozygote and abnormals I/I or II/II. She appeared to be a compound heterozygote.

Figure F-2

Family CyI from Marin et al[69]

Other family studies have revealed II/III and I/III compound heterozygotes who are phenotypically cystinuric.[80] These data are interpreted as evidence for multiple defects

in one allele. If the normal allele is "+" and the mutants are "I", "II", and "III", the genotypes may be described and identified. (Table F-3)

Cystinuria type I seems to be the most common form of the disease.[18,83] Interestingly, types II or III are the more common form in affected Libyan Jews.[118,119]

Table F-3

The Genotypes and Phenotypes of Cystinuria

genotype	name	active intestinal transport cys	lys	arg	urinary excretion of the four amino acids
+/+	normal	present	present	present	normal
+/I	type I heterozygote				normal
+/II	type II heterozygote				++increased
+/III	type III heterozygote				+increased
I/I	type I homozygote	absent	absent	absent	++++increased
II/II	type II homozygote	present	absent	unknown	++++increased
III/III	type III homozygote	present	present	present	++++increased
I/II	genetic compound				++++increased
I/III	genetic compound				++++increased
II/III	genetic compound				++++increased

G. Treatment

The goals of therapy are: (1) To prevent stone formation if it has not yet occurred, (2) To stabilize and hopefully dissolve existing stones. Fulfillment of these goals has been pursued by attempts to decrease production of cystine and/or increase the solubility of the amino acid in the urine. Each of the major therapeutic maneuvers will be explained and evaluated in turn.

(1) Dietary Therapy

Cystine is produced from the essential amino acid methionine by the transsulfuration metabolic pathway. Low methionine or low protein diets have been proposed to lower the amount of cystine which comes to urinary excretion. Dent and Senior reported in 1955 that a low protein diet decreased cystine excretion in their patients.[26] Hershka and co-workers[55] have reported that a chronic low methionine diet, rigorously observed for ten years, and increased fluid intake produced a biochemical "cure" of their patient's cystinuria. Lotz, et al[44] note that a patient on a relatively constant low methionine diet reduced his twenty-four hour urinary cystine excretion by nearly 50%. Zinneman and Jones, on the other hand, found that neither methionine restriction or methionine loading appreciably influenced the urinary excretion of cystine.[113]

A low protein diet is difficult to adhere to and the wisdom of protein-restriction for pediatric cases is questionable. The cystinuria patient should avoid excessive

protein intake. However, a formal low methionine diet is probably not warranted.

(2) Fluids

Within the usual range of urinary pH, about 300mg of cystine will be dissolved in one liter of urine.[26] The principal task of fluid therapy is to solubilize the cystine in a sufficient volume of urine to avoid precipitation. Since many cystinurics excrete up to 1g of cystine per day, they will require 1 liter/300 mg X 1 gram/day = 3400ml of urine flow per day as a minimum (2-3ml/min). To attain this, Dent's group advises patients to consume 600ml (about one pint) of liquid every four hours.[23] This should be regarded as a minimum. The patient is free to select tap-water, tea, beer - whatever he/she wishes. Since urine is concentrated at night, a large drink is taken before retiring. The patient should arise at least once in the middle of the night to void and drink again.

Reports of disease stabilization and stone dissolution from high fluid therapy emphasize the value of this method.[23,96] Fluids remain the first line of therapy for cystinuria. The cystinuric individual should be made to understand that "for him/her, water is to the cystinuric as insulin is to the diabetic."[81] The patient should be encouraged to drink at each visit to the physician. The urine should always be pale in color - never dark yellow. Some patients follow their own urine specific gravities - taking care to maintain it below 1.010. Fluid intake must be increased

in warm climates and during times of vigorous physical activity.

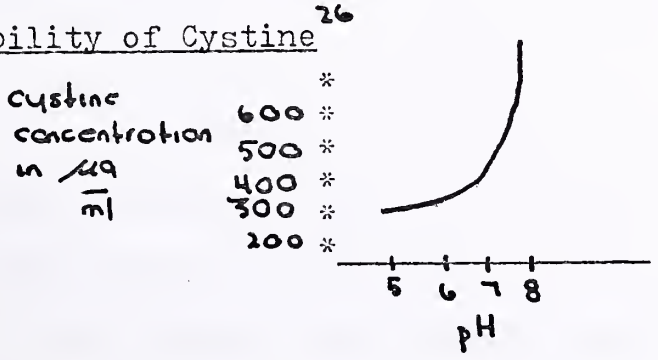
Children present particularly difficult therapeutic problems.[65] Patience and care on the part of parents, sibs, and the physician will be necessary to convince the child to drink adequate volumes. The battle may be lost if the issue is pressed too strongly too soon. The child must be enlisted in his/her own care. Vigorous childhood activity, which increases fluid losses, must be accompanied by adequate hydration.

(3) Alkalinization

The solubility of cystine begins to increase rapidly at a urinary pH above 7.5. (fig. G-1)

Figure G-1

Solubility of Cystine[26]



An alkaline urine has, therefore, been thought to be of value in stone prevention and dissolution. Urinary alkalinization is achieved by day-time ingestion of bicarbonate or citrate preparations (ie Sodium Bicarbonate, Polycitra). Since the value of alkalinization is not realized until a high urine pH is reached, doses of 30g/day of $NaHCO_3$ may be required. A bedtime dose of acetazolamide (250mg to 500mg) is used to achieve nightime alkalinization. Patients

may monitor their own therapy with commercial dipstick pH tests.

Alkalinization is not without danger. Calcium phosphate tends to precipitate in an alkaline urine, thus presidposing to nephrocalcinosis or the deposition of calcium salts on an existing cystine stone.[86] In addition, metabolic alkalosis may be produced. Finally, there may be a contradindication to the obligate cation load for some patients. Because of side-effects and the difficulty in maintaining sufficiently alkaline urine, clinicians differ on the importance of urinary alkalinization in cystinuria.

(4) Penicillamine

Disulfides undergo exchange reactions with thiols and other disulfides. These reactions may be simply represented by the equations

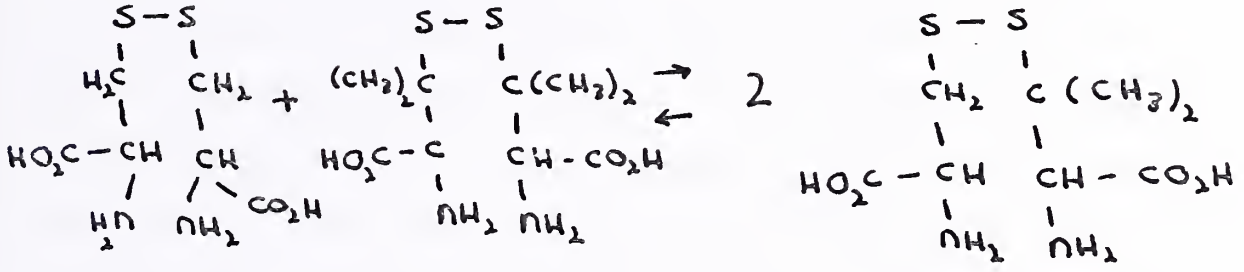
$$R\text{-}S\text{-}S\text{-}R + R_1\text{-}S\text{-}H \rightleftarrows R\text{-}S\text{-}S\text{-}R_1 + R\text{-}S\text{-}H$$

$$R\text{-}S\text{-}S\text{-}R + R_1\text{-}S\text{-}S\text{-}R_1 \rightleftarrows 2R\text{-}S\text{-}S\text{-}R_1$$

The mixed disulfide $RSSR_1$ has different properties than the symmetrical dissulfide RSSR. Preliminary experiments showed that cystine which readily crystallized from the urine of cystinurics could not be crystallized from the same urines at pH 7.2 after the addition of D-penicillamine.[19] The penicillamine-cysteine disulfide is fifty times more soluble than cystine.[64] (see fig. G-2)

Figure G-2

cystine + penicillamine disulfide ⇄ penicillamine-cysteine disulfide



The solubility difference is exploited in therapy for cystinuria.

Crawhall, Scowen, and Watts fed D-penicillamine to two cystinuric patients.[19] They were able to demonstrate that the excretion of cystine was abolished or reduced according to the dose of penicillamine administered. During penicillamine administration two new substances appeared in the urine. They proved to be penicillamine-cysteine disulfide and penicillamine-penicillamine disulfide.

Clinical experience has shown that 1 to 2g/day of penicillamine in the adult, given in four divided doses, can reduce urinary cystine to 100-150mg/day. This is below the range of stone formation. Stabilization of stone disease and stone dissolution may be produced by penillamine administration. The clinical efficacy of the drug has been reported in adults and children. Therapy may be monitored by periodic quantitative amino acid analysis of the urine.

A surprising observation, in the patients with cystinuria, is that total cystine excretion (measured as the total of cysteine present as cystine plus that present as penicillamine -SS- Cysteine) consistently decreased with

increasing doses of penicillamine. In normals, the total amount of half-cystine excreted was increased by penicillamine.[64] There is no satisfactory explanation for this finding.[106]

In addition to cystinuria, penicillamine is used in Wilson's Disease, lead poisoning, and rheumatoid arthritis. A substantial literature is accumulating on the side-effects of the drug.[87] These toxic effects may be considered under the headings of (a) sensitivity reactions, (b) haematologic changes, (c) abnormalities of taste and smell, (d) nephrotoxicity, (e) formation of abnormal antibodies, (f) dermatopathy, (g) connective tissue changes, and (h) other.

(a) One-third to one-half of patients receiving penicillamine suffer from maculopapular skin erruptions, fever, lymphadenopathy, pruritus, and arthropathy within one to ten days of receiving the drug. These reactions disappear on withdrawal of the drug. Reinstitution may be attempted with a "desensitizing" dose of 10mg/day with a gradual increase to full dose. Others reinstitute under coverage of prednisone.

(b) Leukopenia, thrombocytopenia, thrombocytosis, and thrombohemolytic thrombocytopenic purpura[2] have been associated with penicillamine. Therapy must be monitored with frequent platlet and white cell counts. Thrombocytes are frequently counted by machine. Because of clumping a falsely low count may be recorded and a visual check should be made before discontinuing therapy.[29]

(c) Hypogeusia is not infrequently seen. It may be reversed by copper administration and is rarely seen in the therapy for Wilson's Disease.[54] Penicillamine is a pyridoxine antagonist[42,53] and taste abnormalities may generally be reversed by a 50mg/day supplement of vitamin B_6.

(d) Up to one-third of patients suffer from penicillamine induced proteinuria.[29,86,120] This has been reported to progress to frank nephrotic syndrome.[1] The renal biopsy shows focal glomerulitis resembling changes reported in immunologically induced experimental nephritis.[30,52] The drug should be stopped and the patient followed with quantitative urine proteins. Spontaneous resolution is to be expected.

(e) Anti-nuclear and anti-cytoplasmic antibodies have been found in the sera of patients receiving penicillamine.[87] Cutaneous lupus has been reported to be induced by penicillamine.[6] Fatal pulmonary haemorrhages and rapidly progressive glomerulonephritis occurred in three patients with Wilson's Disease who had been treated with penicillamine for two to three and one-half years. The clinical and pathologic abnormalities were similar to those of Goodpasture's Syndrome.[117] Myasthenia has also been reported with use of the drug.[29]

(f) Patients with Wilson's Disease have been reported to suffer from extravasation of blood into the skin - particularly around joints.[102] In addition, a drying and scaling of the facial skin is associated with the drug.[102]

(g) Penicillamine produces an accumulation of poorly cross-linked[70], soluble collagen[48] in the skin. This phenomena appears to be dose related. The drug probably should not be administered in the pre- and post- operative periods.

(h) Nausea, vomiting, malaise, and midepigastric pain have been associated with initiation of D-penicillamine therapy.

As one might expect, the toxicities of penicillamine make one hesitant to prescribe the drug - in spite of its therapeutic efficacy. The two generally accepted indications are: inability to control stone formation on more conservative therapy, and repeated surgery or a nephrectomy while on conservative therapy.[78] The drug should be initiated at low dose with gradual increase to full dosage. Monitoring with a complete blood count and dipstick for urine protein are mandatory.

H. Progress in Therapy

Investigators have tried new drugs in the attempt to improve therapy for cystinuria. This work is given impetus by the difficulty patients have in following prescribed regimens of fluids and alkalinization. The well-known toxic effects of penicillamine have also prompted the search for new drugs.

Mulvaney, et al[73] have reported their experience with six cases of cystinuria treated with acetylcysteine. It has been speculated that this oral agent causes cysteine to be converted to cystine disulfide, which is approximately fifty times more soluble than cystine. The authors report some success in reduction in stone size and number, and control of symptoms.

German researchers have reported on attempts to manage cystinuria with mercaptoproprionyl glycine. The mechanism of action of this oral agent is the thiol disulfide exchange reaction. An early clinical report claimed stabilization or dissolution of stones in seven of nine patients.[116] One drug-associated rash was seen. Nine additional patients have recently been reported to be in excellent control with the drug.[52]

A curiosity is the recently reported first "surgical 'cure' of the disease." A compound heterozygote I/III received a renal transplant for "end-stage kidney failure." Pretransplant dibasic amino acid excretion rates were

clearly abnormal. Excretory rates for the amino acids, measured from samples collected six weeks and twenty months posttransplant, are within normal limits.[58] Renal transplant is not, of course, offered as an appropriate therapeutic intervention for routine cystinuria.

II. THE MANAGEMENT OF CYSTINURIA: PRESENTATION OF DATA FROM A CLINICAL STUDY

A. Goals of the Study

A study was undertaken on the clinical characteristics of cystinuria. There were seven major goals of this study;

1) To identify a population of phenotypic cystinurics
2) To record the major demographic characteristics of this population
3) To document the most common presenting symptoms
4) To establish the average age at the onset of symptoms and the average age of diagnosis
5) To compare the common modalities of therapy for cystinuria to evaluate the most effective mode(s)
6) To study and record the most frequently cited indications for the initiation of penicillamine therapy
7) To record the drug reactions due to penicillamine and demonstrate:
   a) The frequency of drug reactions
   b) The best manner in which to avoid drug reactions
   c) The best manner(s) in which to treat drug reactions once they occur
   d) The frequency with which drug reactions prevent the use of penicillamine in therapy

The principal objectives of this thesis were the fulfillment of goals 5), 6), and 7). Each of the seven goals was fulfilled. In the six sections which follow, the results of each study are presented.

B. Identification of the Population

1. Goal

To identify a population of phenotypic cystinurics

2. Methods

To locate as complete and as representative a population of cystinurics as possible, multiple channels for patient location were used. These efforts were carried out within the constraints of: the limited amount of time allowable for a medical student's thesis, the fact of limited financial resources, and the necessity of all work being conducted by a single researcher.

Initial inquiries were sent to the medical records librarians of nine hospitals: The Children's Hospital of Philadelphia, The Clinical Center of the National Institutes of Health, Coney Island Hospital, The Hospital of the University of Pennsylvania, Johns Hopkins Hospital, Massachusetts General Hospital, The University of Maryland Hospital, The West Haven (Connecticut) Veteran's Administration Hospital, and Yale-New Haven Hospital. Cooperation was readily obtained from medical records librarians at Coney Island, West Haven VA, and Yale-New Haven Hospitals. Through the cooperation of local physicians, the regulations governing outside researchers were modified, and access to records were obtained at Children's Hospital of Philadelphia, Hospital of the University of Pennsylvania, and Massachusetts General Hospital. Approval to examine records at the National Institutes of Health came too late to allow use

of these records. Access to records could not be obtained at Johns Hopkins Hospital or University of Maryland Hospital.

In addition to the aforementioned hospitals, the assistance of seven physicians were solicited. These physicians were; L. Beck, MD (Philadelphia), E. Prien, Jr., MD (Boston), H. Rosen, MD (Brooklyn), L.E. Rosenberg, MD (New Haven), S. Segal, MD (Philadelphia), and M. Yudkoff, MD (Philadelphia). All physicians, who were asked to help locate patients, immediately agreed to do so.

The method used to locate patient records varied with each source. At the West Haven VA and Yale-New Haven Hospitals, the International Classification of Disease code number for cystinuria, 270.1, was used to locate every patient with that diagnosis discharged over the entire period for which records were saved. Then the files of the Yale Genetics Clinic were examined to locate any ambulatory patients missed by searching for discharge diagnoses. Five New Haven physicians allowed access to office records to complete the search for patients: A. Baskin, MD, B. Lytton, MD, L. Rosenberg, MD, S. Thier, MD, and R. Weiss, MD.

Physicians at Coney Island Hospital and Hospital of the University of Pennsylvania provided lists, from memory, of cystinuria patients. The appropriate records were examined. Physicians at Children's Hospital of Philadelphia similarly provided a list from memory but also allowed a search of the ambulatory clinic file - and thus provided several more patients.

In Boston, Dr. E.L. Prien, Jr. provided invaluable assistance by surveying members of four departments of the Massachusetts General Hospital for lists of all cystinuria patients seen at that institution. Ten patients were located at this hospital.

For each patient located, medical records were examined by this writer. These included hospital charts, clinic charts, office records, and correspondence files. Whenever possible the records were personally examined. Trips were made from New Haven to Boston, Brooklyn, and Philadelphia to review charts. When possible, photocopies of records were obtained from community hospitals where members of the cystinuric population had received a portion of their care. If complete records were not available, summaries were used.

Each patient record was analyzed to determine if the patient met the diagnostic criteria of phenotypic cystinuria. These criteria included:

a) The finding of a pure cystine, cystine and calcium oxalate, cystine and calcium phosphate, or cystine and magnesium ammonium phosphate stone in the course of urinary tract lithotomy surgery.

b) Passage of cystine gravel or a cystine stone from the urinary tract.

c) Finding the hexagonal, flat crystals of cystine in a concentrated urine specimen.

d) Urinary cystine excretion greater than or equal to 400 mg/day or 250 mg/g of creatinine.

e) Paper chromotographic or electrophorectic technique showing excessive excretion of cystine, lysine, arginine, and ornithine.

f) A positive nitroprusside test.

A patient was accepted into the study if he/she met at least one of the criteria.

The first calculation made, after a patient was accepted into the study group, was the number of years of follow-up available per patient. These numbers are derived in two ways. The first method involves subtracting the date of the first note in the records from the date of the last to give the number of months of "direct documentation." The second method calls for the subtraction of the birth date from the date of the last note in the record. This second method is of value in giving an indication of approximately how many years of the natural history of cystinuria we observe. This assumes, of course, that an adequate medical history is recorded to cover the years prior to the creation of the record.

3. Results

Medical records on fifty six individuals who carried the diagnosis of cystinuria were eventually obtained. A complete listing of all sources of data may be found in table B-1.

Table B-1

The Sources of Data on Fifty-Six Cystinuria Patients

The number following the name of the source is the total number of patients to whom this source contributed data. The sources are listed alphabetically.

A. Baskin, MD - Office Record (1)
New Haven, Connecticut

L. Beck, MD - Office Record (2)
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Charles Choate Memorial Hospital (1)
Woburn, Massachusetts

Children's Hospital of Philadelphia (2)
Philadelphia, Pennsylvania

Clinica de Nuestra Señora de la Conception (1)
Ciudad Universitario
Madrid, Spain

C.H. Coggins, MD - Office Record (2)
Massachusetts General Hospital
Boston, Massachusetts

Coney Island Hospital (2)
Brooklyn, New York

D. Cornfeld, M D - Office Record (1)
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Danbury Hospital (1)
Danbury, Connecticut

Genetics Clinic (13)
Yale-New Haven Hospital
New Haven, Connecticut

Hamilton, MD - Office Record (1)
Danbury, Connecticut

J. Herrin, MD - Office Record (3)
Massachusetts General Hospital
Boston, Massachusetts

Jack Dempsey Hospital (1)
Farmington, Connecticut

The Jewish Hospital and Medical Center (1)
Brooklyn, New York

S. Kramer, MD - Office Record (2)
Massachusetts General Hospital
Boston, Massachusetts

Laurence and Memorial Hospitals (1)
New London, Connecticut

Long Island Jewish-Hillside Medical Center (1)
New Hyde Park, New York

B. Lytton, MD - Office Record (1)
New Haven, Connecticut

Massachusetts General Hospital (9)
Boston, Massachusetts

Mount Sinai Hospital (1)
New York, New York

Park City Hospital (1)
Bridgeport, Connecticut

E. Prien, Jr., MD - Office Record (2)
Massachusetts General Hospital
Boston, Massachusetts

St. Joseph's Hospital (1)
Carbondale, Pennsylvania

St. Joseph's Hospital (1)
Stamford, Connecticut

S. Segal, MD - Office Record (1)
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

S.O. Thier, MD - Office Record (6)
Yale-New Haven Hospital
New Haven, Connecticut

R. Weiss, MD - Office Record (1)
Yale-New Haven Hospital
New Haven, Connecticut

West Haven Veteran's Administration Hospital (2)
West Haven, Connecticut

Yale Health Plan (1)
New Haven, Connecticut

Yale-New Haven Hospital (29)
New Haven, Connecticut

M. Yudkoff, MD - Office Record (6)
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

The names of the individual patients will not be disclosed.

Care was taken to record the diagnostic criteria for phenotypic cystinuria fulfilled by each patient. Arbitrarily, the time period up to three months following the initial positive diagnostic test was called "initial" work-up. The time following "initial" work-up is called "subsequent" work-up. Table B-2 shows how well the population met the diagnostic criteria "initially" and "subsequently". In addition, we show the number of patients who met only one of the diagnostic criteria.

Table B-2

How the Diagnosis Was Made

Diagnostic Criteria	Met in 0-3 Months		Met After 3 Months		Patients For Whom This Was The Only Criterion	
	No.	%	No.	%	No.	%
a) The finding of a pure cystine, cystine and calcium phosphate, or cystine and magnesium ammonium phosphate stone in the course of urinary tract lithotomy surgery	25 patients	45%	32 patients	57%	3	5%
b) Passage of cystine gravel or stone from the urinary tract	13	23%	19	34%	1	2%
c) Finding cystine crystals in a urine specimen	13	23%	17	30%	1	2%
d) Urinary cystine greater than or equal to 400 mg/day or 250 mg/g of creatinine	20	36%	33	59%	2	4%
e) Paper chromatographic electrophoretic technique showing excessive excretion of cystine, lysine, arginine, and ornithine	12	21%	23	41%	0	0%
f) Positive nitroprusside test	20	36%	29	52%	1	2%

Table B-3 shows the results of the calculation of number of years of available data. This calculation is based on fifty-two of the fifty-six patients for whom data on therapy was available.

Table B-3

The Number of Years of Data Obtained on the Patients

Number of years determined by subtracting the first note in the chart from the last note:

mean 7 years 3 months

range 1 month - 48 years 8 months

Number of years determined by subtracting the birth date from the last note in the chart:

mean 32 years 10 months

range 1 month - 58 years 5 months

4. Discussion

Several writers have previously identified populations of cystinurics. Kretschmer[60], in a 1916 review, was able to find reports of only 107 cases of cystine calculi in a period of more than a century since Wollaston's original report of 1810.[110] In 1931, Lewis[61] summarized 71 cases.

In an attempt to establish accurate incidence figures for cystinuria, Lewis undertook the systematic chemical examination of more than 10,000 college students for the

presence of cystine.[62] In 1932 he reported the identification of 18 individuals as "definitely cystinuric". This suggested that cystinuria uncomplicated by calculi occured more frequently than usually believed.

Larger series of cystinurics have been identified in recent years. Bostrom and Hambraeus have reported extensively on "98 cases of homozygous cystinuria" collected over a 92 year period.[10] MacDonald and Fellers collected sixteen cases for their 1966 report on the efficacy of penicillamine in cystinuria.[66] In 1968, Frimpter reviewed the experience at New York Hospital.[40] An extensive clinical study on eight-nine patients, similar in several of its aims to our work, was recently reported by a Mayo Clinic group.[22]

For our study, fifty-six patients were located. This represents, as far as can be determined, the largest population of cystinurics compiled from multiple medical centers for the purpose of studying the therapy of cystinuria. Table B-2 shows the evidence that we are, in fact, dealing with phenotypic cystinurics. It is reassuring to note that only eight of the fifty-six patients (14%) were admitted to the study group by fulfilling only one of the diagnostic criteria.

The reader is reminded that no claim is made to have compiled a population of "homozygous" cystinurics. It is now known that mixed heterozygotes can present a phenotypic picture similar to a homozygote. The claim of having

compiled a group of homozygotes is unjustified in the absence of detailed biochemical studies and pedigrees.

A mean of 7 years 3 months of direct chart data was obtained per patient (Table B-3). This compares favorably with the Mayo Clinic's mean "follow-up" on their population of 4 years 4.8 months.[22]

C. Demographic Characteristics of the Population

1. Goal

To record the major demographic characteristics of the population of cystinurics.

2. Methods

Data on sex, race, religion, and marital status was recorded based on information obtained from medical records. For those patients who came to surgery, blood typing was done. Blood type distribution for this subpopulation of cystinurics was recorded.

3. Results

It was possible to determine the race of forty-seven patients.

Table C-1

Race	Patients	%
Caucasian	44	94%
Negro	3	6%

The sex of all fifty-six patients was known.

Table C-2

Sex	Patients	%
Male	29	52%
Female	27	48%

Data on religion was obtained for thirty patients. Thirteen were Roman Catholic (43%), nine were Protestant (30%), and eight were Jewish (27%).

Of the fifty patients for whom marital status was recorded, twenty-six were married (52%) and an additional four became married during the time period recorded in the chart (8%). Nineteen were single (38%). One was married and divorced (2%).

Blood types of sixteen patients were known.

Table C-3

Blood Types	Patients	%
A+	4	25 %
B+	4	25 %
B-	1	6 %
O+	7	44 %

4. Discussion

Ninety-four percent of our patients are Caucasian and six percent are Negro. There are occasional reports of cystinuria in Negroes. Fleming, et al[37] have given a detailed account of gastrointestinal malabsorption associated with cystinuria in a fourteen year old Negro boy. Cystinuria

is also reported in Orientals.[79] The population recently reported from the Mayo Clinic is entirely Caucasoid.[22]

One would expect that there would be a random sex distribution in a non-sex linked recessive disorder. This is supported by the male/female = 52%/48% breakdown. The finding of an appropriate sex distribution argues against gross bias in patient identification. Fifty-six percent of MacDonald's patients[66] and Dahlberg's patients were males.[22]

The religious preferences of our population are quite different from national figures. Approximately 130 million Americans are listed as church members. Of this number, 54% are Protestant, 38% Roman Catholic, and 3% are Jewish.[13] The unusually high number of Catholics and Jews in our population is likely a function of the population being drawn from northeastern urban centers.

The most common blood types in Caucasian North Americans are O (46%) and A (42%).[31] The blood type distribution of Table C-3 suggests the normal distribution. However, our numbers are quite small.

D. The Clinical Presentation of Cystinuria

1. Goal

To document the most common presenting symptoms of cystinuria and present this data in a manner useful to the clinician

2. Methods

Traditionally, the terms "chief complaint" or "presenting symptom" have been used to describe the first clue to the detection of a disease. For the clinician interested in cystinuria, these terms are probably inadequate. A significant percentage of newly diagnosed cystinurics have no complaints. A more appropriate term, used by Feinstein, is "iatrotropic stimulus": the symptom or event that provokes a patient to see a doctor.[33]

The data on the most common iatrotropic stimuli is presented in two ways. First, a table presenting each item singly is shown. (Table D-1) Since many patients have more than one impetus to seek medical attention, the number of stimuli exceed the number of patients.

The second table (Table D-2) groups the stimuli into the common patterns reported by patients. The total number of stimuli groups, therefore, equals the number of patients.

3. Results

Table D-1 presents the individual iatrotropic stimuli.

Table D-1

Iatrotropic Stimuli	Number	% Of Patients
Renal colic	28	50%
Haematuria	11	20%
Having an affected family member prompted the patient to come for screening	9	16%
Spontaneous stone passage	7	13%
Urinary tract infection	5	9%
Back pain	3	5%
Anuria	2	4%
Nervousness and dyspepsia	1	2%
Routine urinalysis discovery	1	2%
Screening during a diagnostic work-up for mental retardation	1	2%
Unknown	1	2%

In Table D-2 the association between stimuli are shown.

Table D-2

Iatrotropic Stimuli	Number	% Of Patients
Renal colic	19	34 %
Having an affected family member prompted the patient to come for screening	9	16 %
Haematuria and renal colic	6	11 %
Urinary tract infection	4	7 %
Spontaneous stone passage	3	5 %
Anuria	2	4 %
Renal colic and spontaneous stone passage	2	4 %
Back pain	1	2 %
Back pain and renal colic	1	2 %
Back pain and haematuria and spontaneous stone	1	2 %
Haematuria and spontaneous stone	1	2 %
Haematuria and urinary tract infection	1	2 %
Nervousness and dyspepsia	1	2 %
Routine urinalysis discovery	1	2 %
Screening during a diagnostic work-up for mental retardation	1	2 %
Unknown	1	2 %

4. Discussion

The most common iatratropic stimuli for the cystinuric are renal colic, haematuria, and having an affected family member. Comparison of Tables D-1 and D-2 shows that renal colic often occurs alone while haematuria is rarely a solitary complaint. A significant number of cystinurics are first seen because of an affected family member.

Case reports of cystinuria commonly cite renal colic, haematuria, and stone passage as "presenting complaints". Our findings confirm this experience.

In MacDonald's series of twelve patients[6], seven (58%) "presented because of calculi, two (17%) were traced through their siblings, and two were traced by routine screening of urine samples" undertaken for reasons other than cystinuria. The last patient presented with a suspected urinary-tract infection.

E. The Average Age at Onset of Symptoms and the Average Age of Diagnosis

1. Goals

To establish the average age at the onset of symptoms and the average age at time of diagnosis; To study the value of the family history as part of the original diagnostic work-up.

2. Methods

The vast majority of medical histories identify a first event suggestive of urinary tract pathology. In most cases this event was coincident with the iatrotropic stimulus. The date of occurence of the first symptom, to the nearest month, was recorded. The patients age at the onset of the first symptom was calculated. From this data the mean and median ages at onset of symptoms were derived.

As demonstrated in Tables D-1 and D-2, sixteen percent of patients first came to medical attention because of urinary screening following the discovery of an affected family member. These patients were assymptomatic at the time of initial presentation. Since we are interested in determining the average age at the onset of symptoms, these assymptomatic presentations are not included in the calculations for Tables E-1 and E-2.

The date on which at least one of the diagnostic criteria for phenotypic cystinuria, as listed in section II-B, was fulfilled is considered the "date of diagnosis". The patient's age at diagnosis was determined and an average age at diagnosis was calculated for the population.

Family histories, taken at the time of initial presentation, were studied. From these histories cumulative figures were prepared on the precent of patients with family histories positive for cystinuria or other renal disease. These figures were compiled in order to analyze the value of the family history in the differential diagnosis of stone disease. Only the initial history was studied - not the detailed pedigree typically done by Human Genetics Fellows after the diagnosis was known. Patients who initially presented because of an affected family member were excluded from this calculation since they invariably had positive family histories.

3. Results

Table E-1

Age At Onset Of Symptoms

	Mean	Median
Male	17.3 years	18 years
Female	19.6 years	19 years

Table E-2

Age At Time Of Diagnosis

	Mean	Median
Male	22.3 years	20 years
Female	22.4 years	23 years

Table E-3

Family History, At Initial Presentation, of Patients Presenting with Stone Disease

History Positive For:	Number of Patients	%
Cystinuria	14	29%
Unknown Renal Stone Disease	6	12%
Unknown Renal Disease	1	2%
History negative for renal disease	26	53%
History Unknown	2	4%

4. Discussion

Rosenberg and Scriver report that the initial symptoms of cystine lithiasis "are most common during the third and fourth decades."[86] Thier and Segal advise that "the second and third decades appear to be the peak times for the expression of cystinuria."[106] The median age at onset in the 1977 Mayo Clinic series was 19 years.[22] Our data confirm an average age at onset in the late teens.

There is a three to five year discrepancy between average age at onset of symptoms and age at time of diagnosis. Unfortunately, many cystinuric individuals go undiagnosed or are misdiagnosed for several years after initial symptoms. Cystinuria should be included in the differential diagnosis of stone formation in the younger age groups.

In an autosomal recessive disease, one would expect the disease to occur in only a single generation. These disorders are more frequently seen in the products of consanguinous marriages. It is not suprising, therefore, to find a minority of patients with positive family histories for cystinuria. It is equally clear, however, that a negative family history does not exclude the disease. Fifty percent of the Mayo Clinic's patients

"recalled a family history of colic or urolithiasis in first generation or second generation relatives."[22] Forty-three percent of our patients had a family history positive for cystinuria or other renal disease.

The detailed pedigrees done on cystinuric patients by geneticists may provide clinically useful information. A carefully taken pedigree should be part of the work-up and counseling of these patients.

F. A Comparison of Modes of Therapy

1. Goal

To compare the common modalities of therapy for cystinuria to evaluate the most effective mode(s)

2. Methods

Cystinuria is primarily treated with vigorous fluid ingestion. Fluid ingestion, however, is frequently combined with urinary alkalinizing agents and/or penicillamine. The four most commonly used treatment programs are: (1) fluids alone; (2) fluids and alkali; (3) fluids and penicillamine; (4) fluids, alkali, and penicillamine. We may define these terms:

> "Fluids" means encouraging the patient to consume several liters of fluid per day (the absolute amount varied by clinician) in order to maintain a high volume of urinary output.
>
> "Alkali" includes the use of bicarbonate, citrate, or acetazolamide to alkalinize the urine.
>
> "Penicillamine" is the chelating agent D-penicillamine.

The measurement of the efficacy of these treatments is a difficult task. There is no reasonable way to quantitate

whether any one modality is more effective at making people "feel better". What one can quantitate are indirect measures of the ability of a therapy to aid the patient. In the case of cystinuria, six such measurements, or indices, have been selected. The indices are: rate of urinary tract lithotomy surgery, rate of cystoscopy, rate of occurrence of renal colic, rate of occurrence of urinary tract infections, episodes of spontaneous stone passage, and roentgenographic evidence of change in stone size or number. Each of the indices, save for roentgenographic evidence of stone change, will be expressed as a rate. The indices are defined as follows:

> "Urinary tract lithotomy surgery" includes pelviolithotomy, nephrolithomy, ureterolithotomy, nephrectomy secondary to stone disease, and cystolithotomy.
>
> "Cystoscopy" is examination of the urinary tract by cystoscope.
>
> "Renal Colic" is characteristically visceral pain with fluctuations corresponding to smooth muscle peristalsis produced by thrombosis or dissection of the renal artery, renal infarction, intrarenal mass lesions, the passage of a stone within the collecting system, or thrombosis of the renal vein.[39] We shall restrict ourselves to those incidents of renal colic associated with a stone. The association may be demonstrated by roentgenographic studies, concurrent with the episode of colic, demonstrating the stone; by passage of a stone; or by finding a stone at surgery.
>
> "Urinary tract infection" is manifested by dysuria (discomfort, pain, burning, stinging on urination), urgency, and frequency. Cystitis, on the other hand, produces suprapubic pain and tenderness. Bacteriuria is the hallmark of urinary tract infections. In this study no urinary tract infection will be counted as such unless there is evidence of bacteriuria. One or more of

the following constitute acceptable evidence:

(1) Growth of 10^5 or more bacteria per ml of urine from a clean voided midstream specimen
(2) Growth of 10 or more bacteria per ml of urine from a suprapubic percutaneous aspiration of urine
(3) Readily finding bacteria in a drop or loop of freshly voided uncentrifuged urine examined with an oil immersion objective [56]

"Spontaneous stone passage" is an episode of passing a "stone" or "gravel" per urethra and observed by the patient, nurse, physician, or family member.

Roentgenographic assessment of stone disease was done based on criteria developed by Smith.[99]

(1) Metabolically active urolithiasis is defined by roentgenographic studies, over time, showing either evidence of stone growth or evidence of increase in stone number.
(2) Metabolically stable urolithiasis is defined by roentgenographic studies, over time, showing no change in stone size or number.
(3) Improving stone disease is defined by roentgenographic studies, over time, showing decrease in stone size and/or number.
(4) Indeterminate activity is said to exist when either: a) Films are not available or are inadequate for evaluation of stone disease. b) Surgery or stone passage has occurred between roentgenographic studies changing stone size or number.

The denominator for the computation of the rates of occurrence of the above-defined numerators will be the "patient-year of observation". The number of persons observed and the duration of observation of each person on each therapy has been considered. For example, two persons on fluid therapy alone, for eighteen months each, constitute three patient-years of observation of fluid therapy.[63] The patient-year is particularly useful in the study of cystinuria. One must remember, however, that the patient-year concept is limited by the

inherent assumption that the risk being measured remains constant for any subject during the time of observation.[94]

Life tables are not appropriate for studying the therapy of cystinuria. The cystinuric population's variability of age, sex, and periods of individuals being on therapy makes computation of actuarial life tables quite difficult. In particular, the typical cystinuric patient changes therapy so often that it would be impossible to maintain sufficient patients in the study group for life table analysis.

Having defined numerators (surgery, colic, etc.) and denominators (patient-years) for the indices which will be used, we must answer the question: Which patients constitute the appropriate reference group? It is inappropriate to simply compare cystinuric patients on fluids alone to those, say, on fluids plus penicillamine. One suspects that those patients who have alkali and/or penicillamine added to their fluid therapy have, for the most part, clinically more severe disease than those on fluids alone. The absolute number of therapeutic interventions increase as a function of the inability of more conservative measures to control disease. Data supporting this particular argument is presented in the "Results" section as Table F-1.

If we freely compared, say, penicillamine-treated to nonpenicillamine-treated patients we would be comparing "relatively sick" patients to "relatively well" patients. This would certainly be unreasonable. A method must be found to select-out the patient-years of "relatively sick" cystinurics and compare treatment modalities within this group.

There are two ways to select out the "sicker" cystinuric patients. One may use either "symptomatic" criteria or "treatment" criteria.[36] "Symptomatic" criteria arise from patient symptoms or objective laboratory and x-ray data. Examples of such criteria are:

- only study patients excreting more than an arbitrary number of milligrams of cystine per 24 hours
- study those patients who have x-ray evidence of stones greater than or equal to a certain size

"Treatment" criteria, for choosing more severely affected patients, involve milestones of therapy. Examples of such milestones are:

- study patients cystoscoped more than an arbitrary number of times
- study patients who have more than an arbitrary number of lithotomy operations

The advantages of selecting a reference group by symptomatic criteria are clear. These criteria are not influenced by personal opinions of the physician as to treatment. They probably are the most direct reflections of disease. The most prominent disadvantage is that most forms of symptomatic data are difficult to obtain from medical records. It would be impossible, for example, to use the above cited examples of symptomatic criteria. Stone sizes are not measured and mg/24hour excretions of cystine are not uniformly reported.

"Treatment" criteria for patient selection may be criticized as being subject, in part, to the whim of physicians. They may, however, be defended on the grounds that

treatment usually is at least a partial reflection of the severity of disease. Hopefully, physicians acting in good faith will recommend a therapeutic intervention only when the severity of disease warrants it. Treatment criteria are relatively easy-to-use insofar as charts carefully record operations, cystoscopies, etc..

This writer is acutely aware of the need to select-out an appropriate reference group of cystinurics to compare the various modes of therapy. It is clear that either method of selecting this group is not without fault. Therefore, we will select our reference group of "sick" cystinurics in two ways: one using a treatment criteria and one using a symptomatic criteria. This will generate two reference groups of patient-years. The indices of rate of lithotomy surgery, stone episodes, etc. will be measured in both groups. If the results show the same trends in both groups, it will strengthen the conclusions of this thesis. Some potential critics of our methodology, were only one method of selecting a patient group to be used, thus will be denied an objection.

The treatment criterion for selecting patient-years to be studied is as follows: Those patient-years of patients following at least one urinary tract lithotomy operation will be selected as representing a comparable group of cystinurics. These years will constitute the "treatment criterion" reference group. The underlying assumption is that the need to have had surgery suggests relatively severe disease. Operative procedures are generally easy to identify in medical histories.

The symptomatic criterion for selecting patient-years to be studied is as follows: Those patient-years of patients following at least one hospital admission or physician visit for what is identified as renal colic will be selected as representing a comparable group of cystinurics. These years will constitute the "symptomatic criterion" reference group. Renal colic, in its first appearance, is an identifiable symptom. By including hospital admissions and physician visits, we hope to account for variability in physician willingness to admit a patient to the hospital.

It should be noted that no measures of statistical significance were applied in data analysis. The enthusiasm with which one interprets the results of this study should be tempered, therefore, because of the absence of these statistical measures. The services of a biostatistician will be enlisted if any portion of this thesis comes to subsequent publication.

3. Results

It has been argued, in the immediately preceeding section, that patients were selected to receive penicillamine because they had disease unresponsive to more conservative measures. To test this hypotheses, patient records were searched to identify the reasons given for initiating penicillamine in the thirty-two patients who received the drug. The results are presented in Table F-1.

Table F-1

Reasons for Initiating Penicillamine

There were a total of fifty-seven attempts at initiating this drug in thirty-two individuals.

Indication Given for Initiating Penicillamine	Number of times this indication invoked	% of 57 Attempts
Objective Evidence of Active Disease While On Conservative Therapy		
Roentgenographic Evidence	31	54%
"Unacceptably" high 24 hour urinary cystine	4	7%
Crystalluria	3	5%
"Poor renal function" tests	2	4%
Symptoms or Treatment Suggestive of Uncontrolled Disease While On Conservative Therapy		
Recurrent Colic and/or Stone Passage	30	53%
S/P Lithotomy Surgery or Nephrectomy	19	34%
Recurrent UTIs	2	4%
Problems of Patient Management		
Penicillamine was newly available (mid-1960's)	8	14%
It was hoped that addition of a medication would improve patient compliance with his/her therapy	3	5%
Necessary amount of fluid intake was impractical for the patient	2	4%
Surgery had not completely removed stones	2	4%
Penicillamine was Begun as Part of the Initial Therapy of a Patient never Before Treated	10	18%

Table F-1 demonstrates that the principal reason for initiation of penicillamine was the failure of therapy, in the absence of the drug, to control disease. This reinforces the importance of not simply comparing penicillamine to nonpenicllamine patients. It was necessary to select a comparable group of patient-years.

In Table F-2 we present the number of patient-years in

each of the therapeutic categories for a group selected from our population of cystinurics by the "symptomatic" criterion.

Table F-2

The Distribution of Patient-Years Among the Therapeutic Modalities

Patient-Years of Observation in Patients Following At Least One Hospital Admission or Physician Visit for Renal Colic

Therapeutic Modality	Number of Patients Contributing Years To The Category	Total Patient-Years
Fluids	22 patients	76 patient-years
Fluids/Alkali	22	134.5
Fluids/Penicillamine	18	65.5
Fluids/Alkali/ Penicillamine	12	49.2

The distribution of patient-years was also prepared using a "therapeutic" criterion.

Table F-3

The Distribution of Patient-Years Among the Therapeutic Modalities

Patient-Years of Observation in Patients who have had At Least One Lithotomy Operation

Therapeutic Modality	Number of Patients Contributing Years To The Category	Total Patient-Years
Fluids	16 patients	60.6 patient-years
Fluids/Alkali	24	189.7
Fluids/Penicillamine	16	77
Fluids/Alkali/ Penicillamine	12	47.7

In comparing tables F-2 and F-3, we note that for three of the four modes of therapy there are more patient-years per mode in Table F-3 than in Table F-2. This is contrary to expectation. Episodes of renal colic ought to predate lithotomy operations. Our finding may be explained by the greater care with which operations (a treatment) are recorded in charts than episodes of renal colic (a symptom). In both tables the fluids/alkali method was the most frequently employed and the fluids/alkali/penicillamine method was the least frequently used in treating patients.

The distribution of patient-years among the several therapeutic modalities may now be employed to evaluate the relative efficacies of the different modes. First we will consider the effect of type of therapy on rate of lithotomy operation. This writer suspects that this index in one of the most reliable. Histories tend to be fastidious in identifying operations and procedures by type and date. Operative notes, anesthesia records, and pathology reports further allow careful delineation of each procedure. Table F-4 presents the data for the patients selected by the symptomatic criterion.

Table F-4

The Rate of Lithotomy Surgery

Patient-years following one episode of renal colic

Treatment Modality	Patient-Years	Number of Operations	Operations per Patient-Year
Fluids	76patient-yrs	10	0.13
Fluids/Alkali	134.5	18	0.13
Fluids/Penicillamine	65.5	2	0.03
Fluids/Alkali/ Penicillamine	49.2	0	0

This data suggests that the addition of penicillamine to the therapeutic regimen reduces the number of operations per patient-year. We may attempt the same calculation using patient-years selected by the therapeutic criterion and see if the pattern repeats.

Table F-5

The Rate of Lithotomy Surgery

Patient-years following at least one operation

Treatment Modality	Patient-Years	Number of Operations	Operations per Patient-Year
Fluids	60.6 patient-years	4	0.06
Fluids/Alkali	189.7	22	0.11
Fluids/Penicillamine	77	3	0.04
Fluids/Alkali/ Penicillamine	47.7	0	0

Irrespective of how the patient-years are selected, a pattern emerges which shows that penicillamine seems to

reduce the rate at which cystinuric individuals are operated upon.

The second index of therapeutic efficacy which will be examined is rate of cystoscopy. In Table F-6, where patient-years are selected by the symptomatic criterion, we see that penicillamine reduces the rate at which cystinurics are cystoscoped.

Table F-6

The Rate of Cystoscopy

Patient-years following one episode of renal colic

Treatment Modality	Patient-Years	Number of Procedures	Procedures per Patient-Year
Fluids	76 patient-years	6	0.07
Fluids/Alkali	134.5	21	0.15
Fluids/Penicillamine	65.5	0	0
Fluids/Alkali/ Penicillamine	49.2	0	0

Table F-6 suggests that penicillamine reduces the rate of cystoscopy. This pattern remains if the patient-years are selected by the therapeutic criterion.

Table F-7

The Rate of Cystoscopy

Patient-years following at least one operation

Treatment Modality	Patient-Years	Number of Procedures	Procedures per Patient-Year
Fluids	60.6 patient-years	3	0.04
Fluids/Alkali	189.7	22	0.11
Fluids/Penicillamine	77	0	0
Fluids/Alkali/ Penicillamine	47.7	0	0

The third index which will be used to compare modes of therapy is the rate of occurrence of renal colic. We first present the data of patient-years selected by symptomatic criteria.

Table F-8

The Rate of Renal Colic

Patient-years following one episode of renal colic

Treatment Modality	Patient-Years	Number of Episodes	Episodes per Patient-Year
Fluids	76 patient-years	21	0.27
Fluids/Alkali	134.5	32	0.23
Fluids/Penicillamine	65.5	12	0.18
Fluids/Alkali/ Penicillamine	49.2	4	0.08

Adding alkali and/or penicillamine to the therapeutic regimen decreases the episodes of renal colic. Looking at the data in the treatment reference group confirms this finding.

Table F-9

The Rate of Renal Colic

Patient-years following at least one operation

Treatment Modality	Patient-Years	Number of Episodes	Episodes per Patient-Year
Fluids	60.6 patient-years	10	0.16
Fluids/Alkali	189.7	29	0.15
Fluids/Penicillamine	77	10	0.13
Fluids/Alkali/ Penicillamine	47.7	4	0.08

Tables F-8 and F-9 suggest that one may decrease the number of episodes of renal colic by successively adding alkali and penicillamine to the therapy of cystinuria.

Penicillamine does not, however, appear to be successful in reducing the rate of episodes of spontaneous stone passage or of urinary tract infections. Table F-10 presents the data on spontaneous stone passage (symptomatic criterion).

Table F-10

The Rate of Spontaneous Stone Passage

Patient-years following one episode of renal colic

Treatment Modality	Patient-Years	Number of Episodes	Episodes per Patient-Year
Fluids	76 patient-years	28	0.36
Fluids/Alkali	134.5	29	0.21
Fluids/Penicillamine	65.5	21	0.32
Fluids/Alkali/ Penicillamine	49.2	9	0.18

It is curious that the therapeutic modalities which include alkali have the lower rates of spontaneous stone passage. This pattern recurrs, although it is not as striking, if we look at patient-years selected by the therapeutic criterion.

Table F-11

The Rate of Spontaneous Stone Passage

Patient-years following at least one operation

Treatment Modality	Patient-Years	Number of Episodes	Episodes per Patient-Year
Fluids	60.6 patient-years	12	0.19
Fluids/Alkali	189.7	27	0.14
Fluids/Penicillamine	77	20	0.26
Fluids/Alkali/ Penicillamine	47.7	9	0.18

The fifth index is the rate of urinary tract infection. Urinary tract infections were rarely documented in the medical records. By insisting on culture results or gram stains, reported either directly or in progress notes, very few alleged infections were accepted as valid data. Table F-12 shows that the addition of alkali seems to reduce the rate of urinary tract infections.

Table F-12

The Rate of Urinary Tract Infection

Patient-years following one episode of renal colic

Treatment Modality	Patient-Years	Number of UTIs	UTIs per Patient-Year
Fluids	76 patient-years	7	0.09
Fluids/Alkali	134.5	8	0.05
Fluids/Penicillamine	65.5	7	0.10
Fluids/Alkali/ Penicillamine	49.2	2	0.04

The pattern of Table F-12 is repeated when we look at patient-years following at least one lithotomy operation.

Table F-13

The Rate of Urinary Tract Infection

Patient-years following at least one operation

Treatment Modality	Patient-Years	Number of UTIs	UTIs per Patient-Year
Fluids	60.6 patient-years	5	0.08
Fluids/Alkali	189.7	9	0.04
Fluids/Penicillamine	77	10	0.13
Fluids/Alkali/ Penicillamine	47.7	2	0.04

While penicillamine does not appear to be effective in reducing either the rate of spontaneous stone passage or the rate of urinary tract infection, alkali seems to have a positive effect.

The final index of therapeutic efficacy to be presented is "roentgenographic evidence of change in stone size or number." The derivation of this index is explained in the methods section. Table F-14 presents the data for the

symptomatic criterion reference group. On careful examination, this table displays an intriguing pattern: 1) Penicillamine reduces metabolically active urolithiasis measured by x-rays. 2) Penicillamine increases metabolically stable urolithiasis as measured by x-rays. 3) Penicillamine increases the time periods of improving stone disease as measured by x-rays.

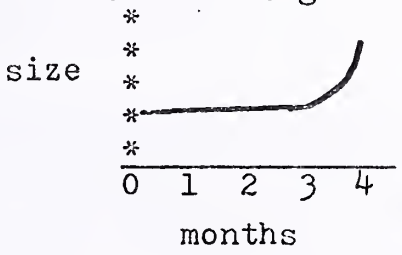
Table F-14

Metabolic Activity of Renal Stone Disease, Measured by X-Rays, In Patients Who Have Had At Least One Episode of Renal Colic

Treatment Modality	Patient-Years	Metabolically Active Urolithiasis		Metabolically Stable Urolithiasis		Improving Stone Disease		Indeterminate Activity	
		Years	% of total years	Years	% of total years	Years	% of total years	Years	% of total years
Fluids	76	25.4	33%	35.8	47%	1.7	2%	13.1	17%
Fluids/Alkali	134.5	62.1	46%	35.6	26%	9.75	7%	27.1	20%
Fluids/Penicillamine	65.5	3.3	5%	34.9	53%	5.8	9%	21.5	33%
Fluids/Alkali/ Penicillamine	49.2	2.8	6%	28.5	58%	4.8	10%	13.1	27%

The reader will notice that no counterpart to Table F-14, using the "treatment" criterion, is presented. Such a table was prepared. It is not, however, presented because in excess of 40% of the patient-years in this table fall in the indeterminate category. Since these "indeterminate" years were unevenly distributed among the treatment modalities, interpretation of data from such a table would be impossible.

A possible source of bias in using x-ray studies is an uneven distribution of time or number of films taken. For example, assume a stone was growing as follows:



If two films were taken, at zero and four months, one would report four months of metabolically active urolithiasis. If, however, three films were taken at zero, three, and four months, one would report three months of "stable" activity and one months of "metabolically active". If the penicillamine groups show noticeably more films per patient-year than the non-penicillamine groups, they might be biased towards under-reporting of "increasing" activity. Table F-15 shows that the rate of films per patient-year varies slightly by treatment modality.

Table F-15

The Number of KUBs + Abdominal Films + IVPs + Retrograde Pyelograms Taken per Patient-Year in Patients Who Have Had At Least One Episode of Renal Colic

Treatment Modality	Patient-Years	Number of Studies	Studies per Patient-Year
Fluids	76 patient-years	110	1.4
Fluids/Alkali	134.5	172	1.3
Fluids/Penicillamine	65.5	108	1.6
Fluids/Alkali/ Penicillamine	49.2	73	1.5

The penicillamine treatment groups do have more studies per patient-year. It is difficult to imagine, however, that such a slight increase in number of x-rays could entirely account for the striking findings of Table F-14.

4. Discussion

Crawhall reported on the ability of penicillamine to reduce urinary cystine concentration in the cystinuric individual in 1963.[19] Two years later, McDonald reported stone dissolution in vivo with the drug.[67] Reports soon appeared detailing the success of drug therapy in series of twelve[66] and fourteen[20] patients. Penicillamine found its way into the therapy of cystinuria.

Since the introduction of penicillamine, there has never been a therapeutic trial carefully comparing the drug to more conservative means of therapy. The logistics of organizing a multicenter randomized double-blind prospective trial are forbidding - and the results would be

several years in coming. One might also expect that clinicians would be hesitant to withold penicillamine, when they believed it was indicated, to satisfy the requirements of a trial.

The principal reason for undertaking this thesis was to design and conduct a trial of the various forms of therapy for cystinuria. The non-concurrent prospective trial which was done utilized six indices of performance to measure therapeutic efficacy. Emerging from the mass of data in tables F-1 through F-15 are three significant findings:

1) Penicillamine, added to either fluids alone or fluids plus alkali, reduces the rates of lithotomy surgery, cystoscopy, and renal colic in a group of cystinuric patients.

2) Alkalinization, added to either fluids alone or fluids plus alkali, slightly reduces the rates of spontaneous stone passage and urinary tract infections.

3) Penicillamine reduces the metabolic activity of cystine renal stone disease as measured by x-rays.

Penicillamine appears to be a useful addition to the therapy of cystinuria when efficacy is measured in the manner utilized in this study.

G. The Use of Penicillamine

1. Goal

To record the drug reactions due to penicillamine and demonstrate the frequency of these reactions, the best manner to avoid and/or treat them, and the frequency with which drug reactions prevent the use of penicillamine for therapy

2. Methods

Urinary cystine values per twenty-four hours were recorded, when available, for all adult patients. This data was plotted on a two dimensional graph as a function of penicillamine dose. This was done to demonstrate the inverse relation of penicillamine dose to urinary cystine concentration.

The outcome of fifty-seven attempts to initiate penicillamine therapy in thirty-two patients were recorded. An outcome was classified, based on chart review, as one of the following: 1) penicillamine stopped because of drug reaction, 2) penicillamine was stopped by a non-compliant patient, 3) penicillamine was stopped because the clinician felt it had fulfilled its task and was no longer needed, 4) penicillamine was thought by the clinician to be inefficacious, 5) penicillamine was continued to the end of the medical record.

A drug reaction was defined as an untoward response following the onset of drug therapy. Some drug reactions are relieved relatively rapidly by cessation of drug therapy. They may even dissipate without cessation of

therapy. Many of these reactions are of the immune-complex, Arthus type (Type III) group ie fever, rash, and joint pain.[3] The nephrotoxic effects of penicillamine, on the other hand, can follow the onset of therapy by many months and dissipate slowly following termination of drug therapy. The reactions to be counted are defined as follows:

"Fever" greater and 99.6° orally or 100.3° rectally measured either by the patient or by medical personel

"Rash" is a maculopapular skin erruption observed and recorded by a physician.

"Arthropathy" in a patient with no previous history of joint disorder will be tabulated.

A "disorder of taste and/or smell" will be defined as the report by the patient of a loss of olfactory or gustatory acuity or symptoms of inexplicable sensations of foul or noxious odors or tastes.

"Leukopenia" is a white blood cell count of less than 5000 cells/ml^3 on at least two occassions in a patient who had, within six months prior to therapy, a white count greater than or equal to 5000 cells/ml^3.

"Thrombocytopenia" is a platlet count of less than 150,000/ml^3 on at least two occassions in a patient who, within six months prior to therapy, had a platlet count of at least 150,000/ml^3.

"Proteinuria" is urinary protein greater than 500 mg/day. (There were no patients with pre-penicillamine urinary protein values greater than 500 mg/day.)

"Glomerulitis" due to penicillamine must be renal biopsy proved.[30,52]

The date of onset of a side-effect was recorded to the nearest day following the first dose of penicillamine in a therapeutic course.

After a documented episode of proteinuria, subsequent

urinary protein values were recorded so that the resolution of the side-effect could be documented.

3. Results

The ability of penicillamine to lower urinary concentration of cystine in the cystinuria patient is well-known.[19,66,67] Figure G-1 is a composite of urinary cystine values, for seventeen adult patients, shown as a function of penicillamine dose. An inverse relation of penicillamine dose to cystine concentration is shown.

Clinical efficacy is not synonymous with low urinary cystine values. For penicillamine to be useful, patients must take the drug chronically. In Table G-2 the outcomes of fifty-seven attempts to initiate penicillamine in thirty-two patients are shown.

Table G-2

The Outcomes of Fifty-Seven Attempts to Initiate Penicillamine In Thirty-Two Patients

The therapy was stopped because of

drug reactions in 29 instances. (51%)

patient non-compliance in 3 instances. (5%)

the physician deeming the drug no longer necessary in 4 instances. (7%)

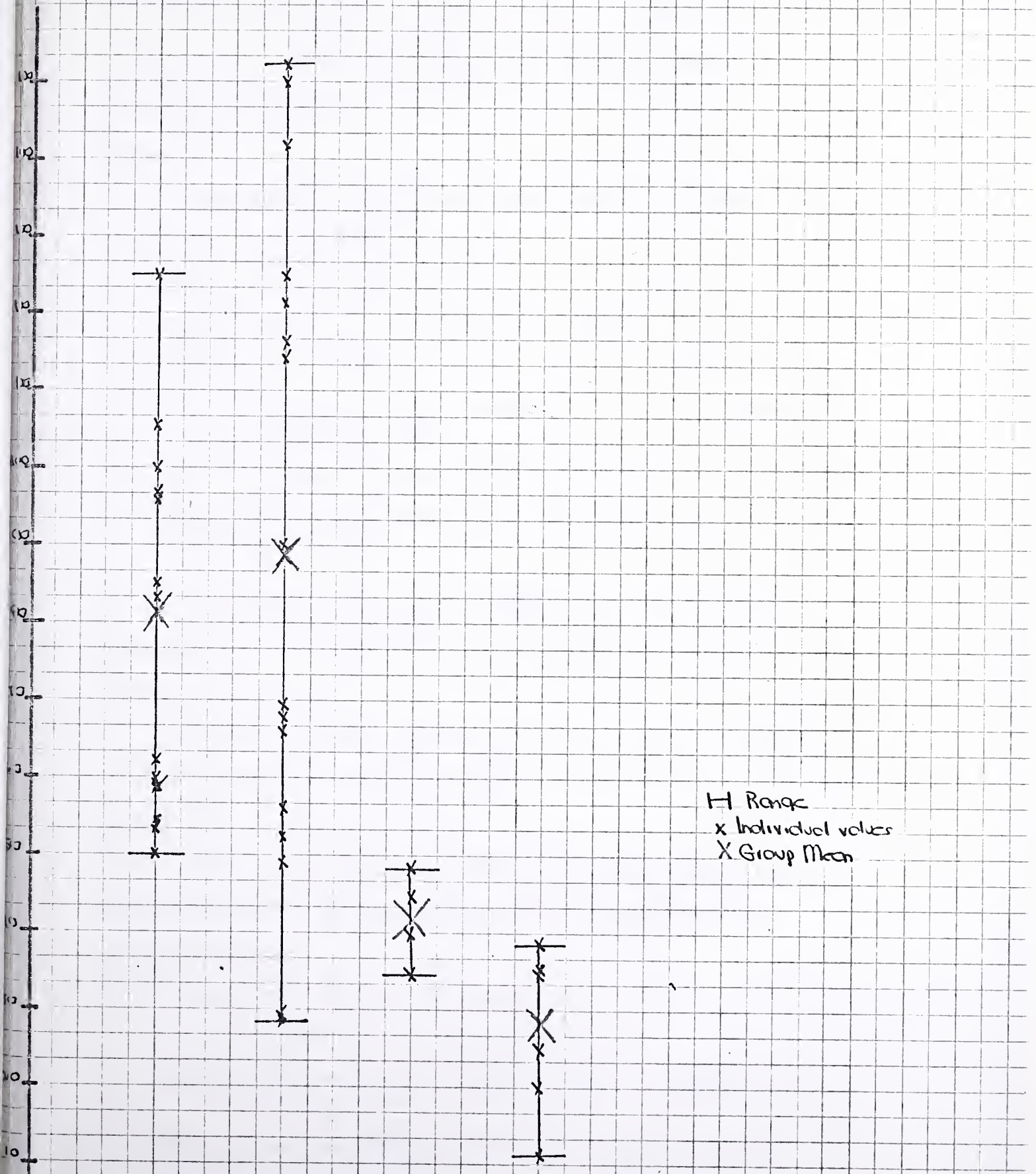
the physician deeming the drug inefficacious in 1 instance. (2%)

The therapy was continued to the end of the chart in 29 instances. (35%)

It is clear that the majority of courses of therapy can not be or are not maintained chronically.

Looking at the issue of therapy initiation in more

The Relation of Cystine Excretion To Dose of Penicillamine in Seventeen Cystinuria Patients


H Range
x Individual values
X Group Mean
Excretion at the time of diagnosis
On a therapeutic regimine which didn't include penicillamine
On 1gm d. of penicillamine
On 2gm d of penicillamine

detail, we see the dismal record of first attempts at initiating therapy.

Table G-3

The Outcome of Thirty-Two Initial Attempts to Begin Penicillamine Therapy in Thirty-Two Patients

The therapy was stopped because of

drug reaction in 18 instances. (56%)

patient non-compliance in 2 instances. (6%)

the physician deeming the drug no longer necessary in 3 instances. (9%)

the physician deeming the drug inefficacious in 1 instance. (3%)

The therapy was continued to the end of the chart in 8 instances. (25%)

It is remarkable that only one-fourth of the patients started on penicillamine are kept on it through our follow-up period.

Attempts to start therapy, when the first attempt failed because of a drug reaction, have a higher success rate.

Table G-4

The Outcome of Twenty-Two Attempts to Start Penicillamine Therapy When the First Attempt Had Failed Because of a Drug Reaction

The therapy was stopped because of a

drug reaction in 11 instances. (50%)

physician deeming the drug no longer necessary in 1 instance. (5%)

The therapy was continued to the end of the chart in 10 instances. (46%)

The drug reactions attributable to penicillamine use in cystinuria are shown in Table G-5. A drug reaction is counted as occurring a maximum of once per patient. For example, if penicillamine were administered three times to an individual, and he/she suffered from a rash each time, this would be counted as one drug reaction. This prevents artificial inflation of statistics - ie we do not count six drug reactions in an individual who was given the drug six times by a stubborn physician.

Table G-5

The Side-Effects of Penicillamine in Thirty-Two Patients

Side-Effect	Number of Episodes	% of 32
Rash	14	44%
Fever	12	38%
Proteinuria	11	34%
Pruritus	7	22%
Arthropathy	5	16%
Adenopathy	4	13%
Glomerulitus	3	9%
Taste/Smell	3	9%
Nausea/Vomiting	2	6%
EKG Changes	1	2%
Headache, Malaise, Midepigastric pain	1	2%
Pulmonary Embolus	1	2%
Thrombocytopenia	0	0%
Leukopenia	0	0%

It is particularly distressing that one-third of individuals taking penicillamine develop documented proteinuria - in excess of 500 mg/day.

The average dates of onset of the side-effects is shown in Table G-6.

Table G-6

Average Time of Onset Of Penicillamine Induced Side-Effects

Side-effects are listed in order of frequency

Side-Effect	Range	Mean	Median
Rash	1-30days	9.3days	9days
Fever	1-30days	10.5days	9days
Proteinuria	1-45months	12.3months	5months
Arthropathy	6-36days	15.8days	10days
Adenopathy	2-21days	11days	10days
Taste/Smell	26-55days	37days	40days
Nausea/Vomiting	10-30days	15.8days	13days
EKG Changes	11 days	*	*
Headache, Malaise, Midepigastric pain	6-18days	*	*
Pulmonary Embolus	8 months	*	*

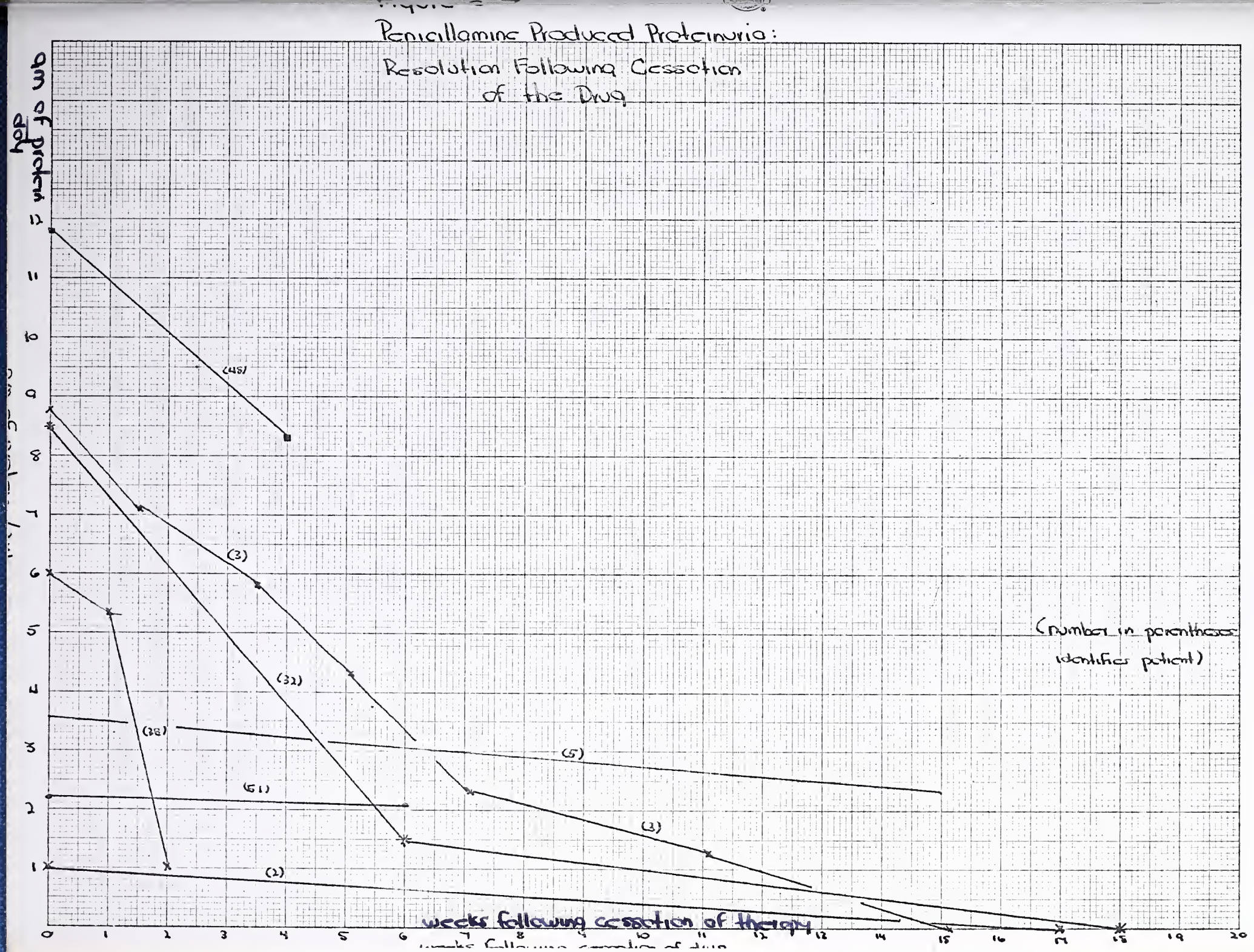
* indicates only one value

Penicillamine induced proteinuria resolves following cessation of the drug. Serial urine proteins, for seven proteinuric patients, are shown in Figure G-7. Sufficient data is available for three patients (2,3,32) to show complete resolution of the proteinuria.

The therapy of acute penicillamine drug reactions in not uniform. Review of patient records discloses no less than

Figure

Penicillamine Produced Proteinuria: Resolution Following Cessation of the Drug



eleven different treatments for drug reactions. The most frequently used therapeutic intervention is stopping the drug. Clinicians have also used, however, various combinations of steroids, antihistamines, and dose adjustments in the therapy of penicillamine side-effects. A few general principals may be discerned from studying clinical experience in treating drug reactions. It was noted that the serum sickness side effects (fever, rash, arthropathy, adenopathy) always successfully resolved when the drug was stopped. Proteinuria was also responsive to removal of penicillamine. In the three instances of taste/smell side effects the co-administration of pyridoxine produced relief.

The management of penicillamine side effects may also be approached prophylactically. Clinicians have tried various dosage schemes to avoid unwanted drug reactions. The "conventional" way of initiating therapy begins with a dose of 250mg/day to 500mg/day and rapidly goes to the full 1 or 2 g/day dose. The "desensitization" technique begins with doses in the 10 mg/day to 25 mg/day range. The dose is raised slowly, every third day, until 1 g/day to 2 g/day is reached at approximately thirty days. Using the "steroid coverage" method involves co-administration of prednisone with penicillamine. In the thirty-two attempts at starting penicillamine therapy in our population, conventional dosage initiation was selected in thirty cases. The success rate is essentially that shown previously in Table G-3.

Twenty-two attempts were made to restart therapy when

the first attempt failed because of a drug reaction. Table G-8 suggests the value of the desensitization technique of therapy initiation following a first failure.

Table G-8

Avoidance of Drug Reactions

In twenty-two attempts to start therapy when the first attempt failed because of drug reaction:

	Manner of Dose Initiation		
	Conventional	Desensitization	All Others
Therapy stopped for			
drug reaction	4 (57%)	3 (30%)	4 (80%)
other reason	1 (14%)		
Therapy not stopped	2 (29%)	7 (70%)	1 (20%)
	7 (100%)	10 (100%)	5 (100%)

4. Discussion

Goodman and Gilman's pharmacology textbook describes d-penicillamine as "relatively nontoxic, and much of the toxicity reported is attributable to the use of the L or DL forms."[44] The clinical literature suggests that this is not the case. In an early report on penicillamine in the treatment of cystinuria,[66] five out of twelve patients developed a skin erruption on the eighth to tenth day of therapy. The same authors repored that two patients had been troubled by transient nausea. Drago, et al report one out of three cystinurics treated with penicillamine was affected by a "confluent macular rash and malaise."[28] The Mayo Clinic group reports on complications of treatment in a population of

forty-three patients.[22] We may adapt this Mayo Clinic data for tabular presentation.

Table G-9

Complications of Penicillamine Treatment in the Mayo Clinic Population of Cystinurics

Adapted by E. Halperin from the article of Dahlberg, et al[22]

Side Effect	Number of Patients	% of 43 patients
Rash ("occasionally accompanied by fever and lymphadenopathy")	12	30%
Taste Abnormalities	6	14%
Proteinuria ("High Grade")	4	9%
Granulocytopenia	1	2%

The data reported in this thesis confirms preceeding clinical literature on the spectrum of penicillamine side-effects. We report, however, a distressingly high frequency of proteinuria. One-third of our population developed this potentially threatening side-effect. Adams, et al first reported nephrotic syndrome associated with penicillamine therapy of Wilson's Disease in 1964.[1] Nephrotoxic effects of penicillamine in cystinuria were reported by Rosenberg and Hayslett in 1967.[55] The histopathology of the renal lesion was defined in later studies.[50,52] Although the renal lesion appeared not to be progressive in our population of cystinurics, a death has been reported of a patient who developed nephrotic syndrome while receiving penicillamine.[102]

Sternlieb and Scheinberg have reported on the

side-effects of penicillamine therapy for Wilson's Disease.[102] The type and frequency of these effects differ somewhat from the cystinuria population. Table G-10, adapted from the work of the Albert Einstein Medical College group, shows the most common side-effects of penicillamine when it is used in the treatment of Wilson's Disease.

Table G-10

Complications of Penicillamine Treatment in a Population with Wilson's Disease

Adapted by E. Halperin from Sternlieb and Scheinberg[102]

Side-Effect	Number of Patients	% of the 33 patients in the population
Rash	6	18%
Extravasation of Blood into skin	6	18%
Leucopenia	5	15%
Fever	4	12%
Drying and scaling of skin of face	4	12%
Thrombocytopenia	3	9%
Adenopathy	2	6%
Nausea	2	6%

H. Summary

A population of fifty-six individuals with phenotypic cystinuria was identified. The medical records of these individuals, obtained from hospitals on the northeastern United States, were examined for a study of the clinical characteristics and treatment of cystinuria. The population proved to be predominately Caucasian with an equal sex distribution. The common iatrotropic stimuli at first presentation are renal colic, haematuria, and having an affected relative. The median age a presentation is approximately 18 years.

A nonconcurrent prospective study was conducted to determine the most effective mode(s) of therapy for cystinuria. Therapy with penicillamine seemed effective in reducing the rate of lithotomy surgery, cystoscopy, and renal colic in our population of cystinurics. The drug also reduced the metabolic activity of renal stone disease as measured by x-rays. Penicillamine was not valuable in reduction of urinary tract infections or episodes of spontaneous stone passage.

Penicillamine is a difficult drug to use. Most patients begun on a therapeutic course of the drug will have the course of treatment terminated by a side-effect. The most common side-effects are rash, fever, and proteinuria. Side-effects may be effectively treated with cessation of the drug. The technique of desensitization frequently permits institution of the drug in an individual who had previously had

therapy terminated because of a side-effect. The type and frequency of side-effects seen when penicillamine is used for treatment of cystinuria differ from the spectrum of side-effects reported when the drug is used in Wilson's Disease.

Penicillamine has been shown to be useful in the treatment of cystinuria. It should, however, be used with caution because of frequent and potentially severe side-effects.

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